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ORIGINAL COMMUNICATION

The persistence of seizures after tumor resection negatively affects survival in low-grade glioma patients: a clinical retrospective study

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Abstract

Introduction Seizures are the most common clinical manifestation of low-grade glioma (LGG). Many papers hypothesized an influence of epilepsy on glioma progression. To our knowledge, no clinical study demonstrated a direct relationship between persistence of epileptic seizures after surgery and overall survival (OS) in LGG patients. The present study aims at investigating the correlation between post-operative seizure outcome and survival in tumor-related epilepsy (TRE) patients.

Methods We performed a retrospective analysis of adult patients affected by TRE who underwent surgery for resection of LGG in a single high-volume neurosurgical center. Seizure outcome was assessed 1 year after surgery and categorized according to Engel classification. Clinical, molecular and radiological features were evaluated in univariate and multivariate analyses to investigate the correlation with OS.

Results A total of 146 patients met the inclusion criteria. Histopathological diagnosis was Diffuse Astrocytoma isocitrate dehydrogenase (IDH) wild type in 16 patients (11%), Diffuse astrocytoma IDH mutated in 89 patients (61%) and oligodendroglioma IDH mutated, 1p 19q codeleted in 41 patients (28%). 1 year after surgery, 103 (70.6%) patients were in Engel class 1. Median duration of follow-up period was 69.5 months. Median OS was 79.3 (72.2–86.4) months in the whole population, while it was 86.8 (78.4–95.2), 63.9 (45.7–82), 63.7 (45.2–82.2) and 47.5 (18.3–76.6) months for patients in Engel class 1, 2, 3 and 4, respectively. In a univariate analysis, Engel class evaluated 1 year after surgery significantly influenced OS ($p < 0.01$). Multivariate analysis showed that OS was independently associated with extent of resection ($p = 0.02$), molecular class ($p < 0.01$) and Engel class ($p = 0.04$).

Conclusions Seizure control 1 year after surgery significantly predicted survival of patients affected by LGG-related epilepsy in a large monocentric retrospective series. Future studies are needed to confirm these results and to assess if an epilepsy-surgical therapeutic approach may improve OS.

Keywords Epilepsy · Extent of resection · Awake craniotomy · Low-grade glioma · Engel class

Introduction

Adult Low-Grade Gliomas (LGG) are rare tumors (incidence of about 1 per 100,000) that generally affect young adults with no or only slight functional disorders. The typical clinical history comprises an initial indolent subclinical phase, followed by continuous tumor growth that determines infiltration of cortical and subcortical functional areas with subsequent onset of neurological impairment. Finally, progression to higher grade of malignancy leads to death [1].

Seizures represent the most common symptom at presentation (60–90%) [2] and frequently show resistance to anti-seizures medications (ASMs). This negatively affects quality of life, so surgical treatment aims at obtaining not only the oncological control of the disease, but also seizure freedom [3].

The primary treatment of LGG where possible should be maximal safe resection of the tumor, as the extent of resection (EOR) has been widely demonstrated to be one of the most important predictive factors, both for overall survival (OS) and for seizure outcome [4–9]. However, resection is often limited by infiltration of eloquent areas and, even in patients in whom an apparently total resection had been

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achieved, recurrence and malignant progression of the tumor are frequently observed.

A growing body of literature suggests that a reciprocal relationship exists between tumor and tumor-related epilepsy (TRE) [10]. Not only the presence of the glioma induces the onset of seizure, but also the epileptic activity influences tumor growth and progression [10]. Glioma progression and epilepsy share common pathogenetic pathways [11]. Moreover, radio- and chemotherapy showed to be effective on epilepsy, even before a response is evident at the imaging, and seizure reduction is a sign of response to therapy [12, 13]. Some ASMs have been hypothesized to have an anti-tumoral effect [10].

Despite all these data coming from literature, this relationship has not been clearly documented in the clinical setting. Thus, the present study aims at investigating the correlation between seizure outcome after surgery and OS in patients affected by LGG-related epilepsy.

Methods

Study population

We retrospectively analyzed clinical and imaging data from adult patients with tumor-related epilepsy who underwent surgery for LGG in a single institution between 2000 and 2018 (Department of Neurosurgery, Udine University Hospital).

Patients were included in the present study according to the following criteria:

- Age ≥ 18 years
- Tumor-related epilepsy
- Pre-operative MRI suggestive of supratentorial LGG
- No previous surgery
- No pre-operative chemo- or radiotherapy
- At least 18 months of follow-up
- Objective evaluation of EOR preoperatively and post-operatively on MRI images in DICOM format based on T2-weighted MRI sequences
- Revision of histopathological specimens by using the 2016 WHO Classification of Tumors of the Central Nervous System [14].

Needle biopsies were excluded from the study. The local Ethics Committee, Comitato Etico Unico Regionale del Friuli Venezia Giulia, approved this investigation (Protocol N.0036567/P/GEN/EGAS, ID study 2540). Considering the retrospective nature of the study, written consent to participate in the study was not applicable. Written informed consent was obtained for surgery.

Clinical data

Seizures were classified according to the recent ILAE recommendations [15]. All the patients were evaluated with standard EEG registrations. The frequency of epileptic seizures and the anti-epileptic treatments were also recorded. Seizure outcome was evaluated 1 year after surgery and categorized according to Engel classification [16]. Patients in Class I are free from disabling seizures (excluding early post-operative seizures), patients in Class II have only rare disabling seizures, in Class III the patients had a worthwhile improvement of seizures after surgery, while the patients in Class IV have not had a worthwhile improvement after surgery.

According to international guidelines, no adjuvant treatment was performed after surgery. When tumor progression occurred, the type of adjuvant treatment was chosen on a case-by-case basis.

Volumetric analysis

All pre- and post-operative tumor segmentations were performed manually across axial T2-weighted slices.

The EOR was computed on 3D T2-weighted MRI by applying the following formula: (pre-operative tumor volume−post-operative tumor volume)/pre-operative tumor volume) [17]. Post-operative MRI was performed 4 months after surgery, to reduce the risk of misinterpretation of tumor volume resulting from post-surgical edema.

Histological and molecular analysis

All histological samples were reviewed according to the 2016 World Health Organization (WHO) classification [18]. The following molecular markers were evaluated (as previously described [19]): ATRX, p53, IDH1 and IDH2 mutation, MGMT methylation, 1p 19q codeletion.

Statistical analysis

Continuous variables were summarized by mean and standard deviation or median and range, as appropriate. Dichotomous or categorical variables were summarized by frequencies and percentages. Statistically significant differences on distribution were evaluated performing chi-squared test for categorical variables, and *t* test, Wilcoxon rank-sum tests or Kruskal–Wallis for continuous variables, as appropriate.

Overall survival (OS) was defined as freedom from all-cause mortality. OS was estimated using the Kaplan–Meier approach. Univariate and multivariate Cox regression models were performed to identify the association between any

variable and OS as outcome variables, after the proportional hazards assumption had been verified. Statistically significant ($p < 0.05$) variables at univariate analysis were included in multivariate analysis.

The primary endpoint was the effect of seizure outcome classified according to Engel class on OS.

All analyses were conducted using SYSTAT software (version 12.02.00, SYSTAT software, Inc. 2007).

Results

Clinical and radiological data are summarized in Table 1. A total of 146 patients met the inclusion criteria, 57 (39%) of them were females. Median age at the time of surgery was 38.5 years. 1 year after surgery, 103 patients (70.5%) were seizure free (Engel class I). Twenty (13.7%), 17 (11.6%) and 6 (4.1%) patients were graded as Engel class II, III and IV, respectively. No recurrence or progression of disease was detected, at that time so no patient had any adjuvant treatment in the first year after surgery.

Median duration of follow-up period was 69.5 months (13–239). During the follow-up period, 73 (50%) patients died. All the deaths were caused by tumor progression. The estimated survival, according to Kaplan–Meier approach, at 3, 5 and 10 years (Table 2) was 80.1% (72.7–85.7), 60.3% (51.9–67.7) and 20.5% (14.4–27.4) respectively (Fig. 1). Median OS was 79.3 (72.2–86.4) months in the whole population, while it was 86.8 (78.4–95.2), 63.9 (45.7–82), 63.7 (45.2–82.2) and 47.5 (18.3–76.6) months for patients in Engel class 1, 2, 3 and 4, respectively. Engel class evaluated 1 year after surgery influences OS ($p < 0.01$) (Table 3).

Median pre-operative tumoral volume on T2-weighted sequence was 48 cm^3, while median EOR was 87% (49–100), with median residual tumor of 7.5 cm^3. The histopathological diagnosis according to WHO 2016 classification was Diffuse Astrocytoma isocitrate dehydrogenase (IDH) wild type in 16 patients (11%), Diffuse astrocytoma IDH mutated in 89 patients (61%) and Oligodendroglioma IDH mutated, 1p 19q codeleted in 41 patients (28%). Results of multivariate analysis (Table 3) showed that OS was independently associated with EOR ($p = 0.02$), molecular diagnosis according to WHO 2016 classification ($p < 0.01$) and Engel class ($p = 0.04$).

Discussion

This retrospective analysis shows that the persistence of seizures is an independent predictive factor of worse OS. This result is independent from EOR, radiological data and molecular features considered in this study. To our knowledge, this is the first study reporting seizure control after surgery as an independent predictor of long-term oncological outcome.

From an epileptological point of view, EOR and radiological features have been associated with seizure outcome in LGG [6, 7, 20–22]. Moreover, IDH mutation [23] and many other mutations have been associated to epilepsy in LGG [11, 24]. Persistence of seizures has been related to early recurrence of disease in patients who underwent surgical resection of LGG [25]. Nevertheless, to our knowledge, no previous study evaluated the effect of seizure outcome on long-term OS.

A lower EOR, which is a predictive element both of seizure persistence after surgery and of worse OS. Nevertheless, Engel class predicts OS also independently from EOR at the multivariate analysis.

Pre- and post-operative management of TRE widely varies among different Hospitals. After surgery, as suggested by a recent review [26], ASMs may be progressively tapered and discontinued if patient remains seizure free for at least 1–2 years. Clinical and radiological follow-ups are performed at 1, 3, 6 months and 1 year after surgery; then yearly. In this case series, the administered ASMs do not influence seizure outcome after surgery or OS.

It has been recently demonstrated that gliomas can induce the creation of neuron-glia synapses, whose activation leads to glioma proliferation [27]. Interventions that target this synaptic transmission could slow down tumor growth. A clinical trial that explores the anti-tumoral effect of perampanel, a non-competitive AMPA receptor blocker gave promising results [28]. It may be hypothesized that persisting epileptic activity may promote tumor progression through this cellular pathway, that represents a link between neuronal activity and glioma.

Future prospective multicentric studies with a larger population are needed to confirm that seizure persistence is an independent predictor of OS. Moreover, it should be evaluated if a more accurate pre-operative assessment of epileptic focus and a more aggressive treatment of TRE could improve OS in LGG patients. For example, a clinical trial should evaluate the long-term effect of AMPA receptor blocker or if epilepsy-surgical therapeutic approach (for example, electrocorticography-guided resection [29] or hippocampectomy for temporal LGG [30]) in this group of patients may improve OS.

Limitations

The main limitation of this work is its retrospective design.

The retrospective nature of our study, for example, did not permit to test the hypothesis that, in patients seizure free for the first year after surgery, recurrence of epilepsy can lead to earlier recognition of tumor recurrence or progression.

Table 1 Clinical, radiological and molecular characteristics of the study population

Parameter	Value
No. of patients	146
Age	38.5 years (19–75)
Sex	
Male	90 (61.6)
Female	56 (38.4)
Seizure semiology	
Generalized	88 (60.3)
Focal to bilateral tonic–clonic	12 (8.2)
Absence	9 (6.2)
Bilateral motor	67 (45.9)
Focal	58 (39.7)
Focal motor	21 (14.4)
Non-motor autonomic	4 (2.7)
Non-motor cognitive	12 (8.2)
Non-motor emotional	3 (2.1)
Non-motor sensory	18 (12.3)
Pre-operative seizure frequency	
Daily	11 (7.5)
Weekly	50 (34.3)
Monthly	85 (58.2)
Tumor side	
Left	81 (55.5)
Right	65 (44.5)
Tumor site	
Frontal	47 (32.2)
Parietal	19 (13)
Temporal	23 (15.8)
Insular	57 (39)
Pre-operative tumoral volume on T2WI (cm^3)	48 (6–250)
Pre-operative ΔT2T1 MRI index, (cm^3)	15 (0–95)
Extent of resection	87 (49–100)
Post-operative residual tumor volume on T2WI (cm^3)	7.5 (0–125)
Diagnosis WHO 2016	
DA IDHwt	16 (11)
DA IDHmt	89 (61)
OD IDHmt 1p19q cod	41 (28)
Engel class (12 months after surgery)	
1	103 (70.6)
2	20 (13.7)
3	17 (11.6)
4	6 (4.1)
Seizure outcome for each histologic diagnosis	
DA IDHwt	16
Engel class 1	8 (50)
Engel class 2	3 (18.8)
Engel class 3	3 (18.8)
Engel class 4	2 (12.5)
DA IDHmt	89
Engel class 1	61 (68.5)
Engel class 2	12 (13.5)
Engel class 3	13 (14.6)
Engel class 4	3 (3.4)
OD IDHmt 1p19q cod	41
Engel class 1	34 (82.9)
Engel class 2	5 (12.2)
Engel class 3	1 (2.4)
Engel class 4	1 (2.4)
Clinical follow-up	
Median follow-up, months	69.5 (13–239)
Patient deaths	73 (50)
Patients with progression of disease	109 (74.7)
Adjuvant treatments	
Radiotherapy	85 (58.2)
Chemotherapy	92 (63)
Second surgery	63 (43.2)
Mean survival time, months (confidence interval)	
Whole population	79.3 (72.2–86.4)
Engel class 1	86.8 (78.4–95.2)
Engel class 2	63.9 (45.7–82)
Engel class 3	63.7 (45.2–82.2)
Engel class 4	47.5 (18.3–76.6)

Characteristics of the study population are described using means (standard deviation) or median and range for continuous variables, number of cases with relative percentages reported in parentheses for categorical variables. Extent of Resection (EOR) is computed as described in the text

ΔT2T1 MRI index volumetric difference between pre-operative tumor volumes on T2- and T1-weighted MRI images, *EOR* extent of surgical resection, *DA IDHwt* diffuse astrocytoma isocitrate dehydrogenase wild type, *DA IDHmt* diffuse astrocytoma isocitrate dehydrogenase mutated, *OD IDHmt 1p19q cod* oligodendroglioma isocitrate dehydrogenase mutated, 1p 19q codeleted

However, in our experience, this rarely happens, as patients are followed on a regularly basis.

The fact that the whole case series have been collected in a single center may be considered a limitation to the generalizability of the results. However, on the other hand, this is a guarantee of a unified attitude for seizures treatment and for neurosurgical practice.

Moreover, the time span of the study is relatively wide, and technology [31] and ability of the surgeon have progressively improved. This effect is indirectly quantified by the increase of EOR that was associated with the evolution of the surgical intraoperative technique [32]. As a matter of fact, the improvement of the intraoperative techniques (the use of real time neuropsychological testing during awake craniotomy [33], intraoperative navigation with tractography

Table 2 Overall survival at 3, 5 and 10 years after surgery

Overall survival % (95%CI)	Whole population	Engel class 1	Engel class 2	Engel class 3	Engel class 4
3 years	80.1 (72.7–85.7)	88.3 (80.4–93.2)	70 (45.1–85.3)	52.9 (27.6–73)	50 (11.1–80.4)
5 years	60.3 (51.9–67.7)	69.9 (60–77.8)	35 (15.7–55.2)	41.2 (18.6–62.6)	19.2 (4.6–67.6)
10 years	20.5 (14.4–27.4)	23.3 (15.7–31.8)	20 (6.2–39.3)	11.8 (2–31.2)	NA

Table showing overall survival at 3, 5 and 10 years after surgery

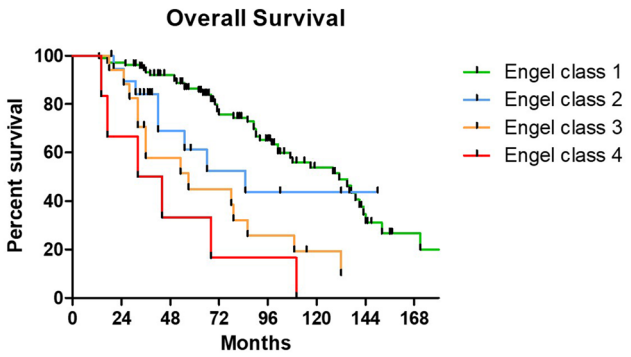

Fig. 1 Overall survival stratified according to Engel class 1 year after surgery, following a Kaplan–Meier approach. Log-rank (Mantel–Cox) test ($p < 0.0001$)

and functional MRI images [5]) significantly influences the EOR.

Molecular analysis included a limited group of targets: ATRX, p53, IDH1 and IDH2 mutation, MGMT methylation, 1p 19q codeletion. Today, we are able to evaluate many other biological features of the tumor. A wider assessment of molecular features of LGG could possibly be able to discover mutations associated both with seizure outcome and survival [11]. This will be evaluated with future studies. The analysis of survival might have been influenced by the presence of sixteen patients affected from DA IDHwt, a molecular subgroup which has a heterogenous clinical evolution [34, 35], but generally considered similar to high-grade glioma. A larger multicentric study may improve the reliability of the present findings,

Table 3 Predictors of overall survival univariate and multivariate analyses

Variable	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	*p* value	Odds ratio	95% CI	*p* value
Engel class at 1 year			**< 0.01**			**0.04**
1	1					
2	1.43	0.66–3.09				
3	3.07	1.32–7.14				
4	5.43	1.04–28.43				
Pathological diagnosis [14]			**0.02**			**< 0.01**
OD IDHmt 1p19q cod	1					
DA IDHwt	3.04	1.13–8.21				
DA IDHmt	1.47	0.89–2.41				
Pre-operative Tumoral Volume computed on T2-weighted images, cm^3			**< 0.01**			0.21
Residual tumor, cm^3			**< 0.01**			0.1
EOR			**< 0.01**			**0.02**
Anti-seizures medications			0.44			
Radiotherapy (only patients with progression of disease)			0.38			
Chemotherapy (only patients with progression of disease)			0.28			
Second surgery (only patients with progression of disease)			0.74			

Table showing the influence of different factors on overall survival as per univariate survival analysis and multivariate analysis. Boldfacing represents statistically significant results ($p < 0.05$). For adjuvant treatments (radiotherapy, chemotherapy and second surgery) only patients with progression of disease were considered for statistical analysis

PO deficit post-operative deficit, *6-m deficit* deficit 6 months after surgery, *MRI* magnetic resonance image, *MRI Index ΔVT1–T2* difference between pre-operative tumoral volume on postcontrast T1-weighted and T2-weighted images, *EOR* extent of resection, *OS* overall survival, *DA IDHwt* diffuse astrocytoma isocitrate dehydrogenase wild type, *DA IDHmt* diffuse astrocytoma isocitrate dehydrogenase mutated, *OD IDHmt 1p19q cod* oligodendroglioma isocitrate dehydrogenase mutated, 1p 19q codeleted

allowing a separate analysis of each of the molecular subgroups of LGG.

Conclusions

This study demonstrated that seizure outcome after surgery for resection of newly diagnosed LGG is an independent predictor of OS in a large monocentric retrospective case series. Future studies are needed to replicate the same result in other contexts and to evaluate if an epilepsy-surgical therapeutic approach may increase OS.

Author contributions Manuscript drafting: EM, CV, GP, GLG, TI. Conception of the work: EM, GP, MS, TI. Data acquisition, analysis and interpretation: GP, CL, RB. Statistical analysis: EM, CV. Critical revision: GLG, MS, GS, GLR, TI.

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Availability of data and material Data will be available under request to the corresponding author.

Code availability Not applicable.

Declarations

Conflicts of interest The authors declare no conflict of interest.

Ethical approval The local Ethics Committee, Comitato Etico Unico Regionale del Friuli Venezia Giulia, approved this investigation (Protocol N.0036567/P/GEN/EGAS, ID study 2540).

Consent to participate Considering the retrospective nature of the study, written consent to participate in the study was not applicable. Written informed consent was obtained for surgery.

Consent for publication Not applicable. No patient is recognizable in any figure or in the manuscript.

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