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Surgery for insular low-grade glioma: predictors of postoperative seizure outcome

Clinical article

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Object. Although a number of recent studies on the surgical treatment of insular low-grade glioma (LGG) have demonstrated that aggressive resection leads to increased overall patient survival and decreased malignant progression, less attention has been given to the results with respect to tumor-related epilepsy. The aim of this investigation was to evaluate the impact of volumetric, histological, and intraoperative neurophysiological factors on seizure outcome in patients with insular LGG.

Methods. The authors evaluated predictors of seizure outcome with special emphasis on both the extent of tumor resection (EOR) and the tumor's infiltrative pattern quantified by computing the difference between the preoperative T2- and T1-weighted MR images (ΔVT2T1) in 52 patients with preoperative drug-resistant epilepsy.

Results. The 12-month postoperative seizure outcome (Engel class) was as follows: seizure free (Class I), 67.31%; rare seizures (Class II), 7.69%; meaningful seizure improvement (Class III), 15.38%; and no improvement or worsening (Class IV), 9.62%. Poor seizure control was more common in patients with a longer preoperative seizure history ($p < 0.002$) and higher frequency of seizures ($p = 0.008$). Better seizure control was achieved in cases with EOR ≥ 90% ($p < 0.001$) and ΔVT2T1 < 30 cm^3 ($p < 0.001$). In the final model, ΔVT2T1 proved to be the strongest independent predictor of seizure outcome in insular LGG patients ($p < 0.0001$).

Conclusions. No or little postoperative seizure improvement occurs mainly in cases with a prevalent infiltrative tumor growth pattern, expressed by high ΔVT2T1 values, which consequently reflects a smaller EOR.
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Key Words • **low-grade glioma** • **postoperative seizure** • **insula** • **extent of resection** • **brain mapping** • **awake surgery** • **oncology**

For a long time, the insula has fascinated anatomists, physiologists, and surgeons because of its complex role and technically challenging access.[3,13,35,38,50,53–55,67] Following the publication of Yaşargil et al., thanks to technical developments and a better understanding of insular functional anatomy, some experiences of insular surgery have recently been reported.[13,20,33,50,53,55,64,67,69] However, to date, there are few data in the literature concerning the epileptological outcome of surgery in patients with insular low-grade gliomas (LGGs).[10,13,17,19,29,45,62,67] Drug-resistant tumor-related epilepsy is observed in approximately 15% of patients with insular LGG, producing a significant impact on patients' quality of life and possibly causing cognitive impairment.[13,24,30] Moreover, seizure control has been reported to be achieved in a percentage ranging between 76% and 90% of cases after insular glioma surgery with perilesional cortical resection.[13,25,45,54,69]

The role of the insula in epilepsy has been a matter of debate for several decades because of its multiple connections with the amygdala, the hippocampus, the olfactory cortex, the entorhinal cortex, and the cingulate gyrus.[35] Recent data appear to confirm the involvement of the insular

Abbreviations used in this paper: AED = antiepileptic drug; ECoG = electrocorticography; EEG = electroencephalography; EOR = extent of resection; ILAE = International League Against Epilepsy; LGG = low-grade glioma; ΔVT2T1 = difference between preoperative tumor volumes on T2- and T1-weighted MRI.

cortex in drug-resistant tumor-related epilepsy.[3,17,25,26,37,60] Interestingly, it was demonstrated that an extensive resection performed at the time of the initial diagnosis constitutes the major favorable prognostic factor in improving patients' overall survival and postoperative seizure outcome.[13,33,37,50,54,55,63,64,69] However, etiology and treatment strategies are still a matter of debate,[61] and, given the lack of strong evidence to predict seizure outcomes, decision-making still varies across surgical centers.

In the present retrospective study, we investigated the impact of surgical variables on seizure outcome, with special emphasis on the role of the extent of resection (EOR) achieved and the infiltrative tumor growth pattern expressed by the difference between preoperative tumor volumes on T2- and T1-weighted MRI (ΔVT2T1).

Methods

Patient Population

For the present investigation, we selected a series of 52 cases involving adult patients with LGG of the insula, who underwent surgery at our institute between January 2000 and May 2011. In all cases, seizure was the initial symptom.

Before surgery, all the patients continued to experience seizures despite therapy with 2–3 antiepileptic drugs (AEDs), resulting in a drug-resistant epilepsy, according to the International League Against Epilepsy (ILAE) definition, proposed by the task force of the ILAE Commission on therapeutic strategies.[32]

Preoperative and postoperative neurological status, seizure semiology and frequency, preoperative electroencephalographic (EEG) recordings, pre- and postoperative MRI findings, and intraoperative electrophysiological data were reviewed retrospectively. Histological type was determined according to the WHO brain tumor classification.[35]

All patients were evaluated at 1, 3, 6, and 12 months after surgery, on anticonvulsant therapy, using the Engel classification of seizures (Class I, seizure free or only auras since surgery; Class II, rare seizures; Class III, meaningful seizure improvement; and Class IV, no seizure improvement or worsening).[21] Engel class at last follow-up was used to compute predictors of postoperative seizure outcome.

The present study was approved by the human research ethics committee of the Azienda Ospedaliero-Universitaria Santa Maria della Misericordia.

Preoperative EEG Recordings

All patients underwent a preoperative 30-minute EEG examination (32-channel EB Neuro Mizar Sirius system with Galileo NT software, EB Neuro), according to the 10–20 International System, with hyperventilation and photic stimulation. Two experienced independent neurophysiologists (G.P. and R.B.), blinded to patients' outcome, reviewed the preoperative EEG recordings and scored them as "normal" (N), "slow" (S), or "epileptic" (E). In detail, 3 main EEG patterns were identified as follows. 1) A normal EEG pattern (N) was characterized by a background activity of alpha or faster rhythms, without focal or diffuse slowing. Focal and diffuse epileptiform discharges (that is, spikes, polyspikes, spike-and-wave and polyspike-and-wave complexes) were absent. 2) A slow EEG pattern (S) was characterized by a background of alpha with focal or multifocal theta or delta activity. A wakefulness EEG pattern with a background of alpha mixed with diffuse theta-delta activity was also classified as "slow." Epileptiform activity was not present. 3) An epileptic EEG pattern (E) was characterized by a background of alpha with faster rhythms or alpha mixed with slower activity. Localized or diffused epileptic features (that is, spikes, polyspikes, spike-and-wave and polyspike-and-wave complexes) were recorded.

Surgical Procedure and Intraoperative Electrocorticography

Intraoperative cortical and subcortical electrical stimulation was employed in all cases, according to the intraoperative technique previously described by Duffau[12] and based on the methodology of Berger and Ojemann.[5,6,39,40] Motor evoked potentials (MEPs) and somatosensory evoked potentials (SSEPs) were also recorded during surgery, to continuously monitor the integrity of motor and somatosensory pathways (64-channel Eclipse Neurovascular Workstation, Axon Systems, Inc.; 32-channel video polygraphic station, Brain Quick SystemPlus, MicroMed). The selection of the anesthesiological protocol was based on the preoperative evaluation of hemispheric dominance. Awake craniotomy was performed in all dominant locations, following the methodology previously described by Skrap and colleagues.[55] A neuronavigation system (Medtronic StealthStation) was used in all cases. Intraoperative scalp EEG was recorded mainly to assess the steadiness of general anesthesia or changes in wakefulness during awake surgery, while intraoperative electrocorticography (ECoG) was used in all cases to monitor the occurrence of after-discharge phenomena, electrical, and electro-clinical seizures. For ECoG, silicon strips with 4 or 8 electrodes and an intercontact distance of 10 mm were placed on the exposed lesional tissue and its surroundings, after opening of the dura mater. ECoG was recorded during a pre-resection phase (for at least 10 minutes), a resection phase, and at the end of resection (for at least 10 minutes). The low-frequency filter was set at 1 Hz, the high-frequency filter as set at 80 Hz, and the gain was between 200 and 400 μV, depending on the amplitude of the background and discharges. Two independent trained neurophysiologists (G.P. and R.B.), blinded to patients' outcome, reviewed the pre-resection ECoG recordings off-line. They were scored as "normal" if epileptiform activity (spikes, polyspikes, spikes-and-waves and polyspike-and-wave complexes) was absent (ECoG Pattern N). Otherwise, ECoG recordings were considered pathological and classified using scoring criteria mainly on the basis of those identified by Palmini and coworkers.[7,41,42] In detail 2 main pathological ECoG patterns were identified: 1) ECoG Pattern B was characterized by the presence of a sudden occurrence of spikes for at least 1 second, with a frequency of 10 Hz or more. 2) ECoG Pattern C was characterized by spikes occurring rhythmically at regular time intervals for at least 10 seconds, the interval between 2 successive spikes being 1 second at the most.

The goal of surgery was gross-total resection of the tumor, when technically feasible. Subtotal resection was performed due to tumor involvement of eloquent areas, as demonstrated by intraoperative stimulation mapping.

Volumetric Analysis

All pre- and postoperative tumor segmentations were performed manually across axial MRI slices by using the OSIRIX software tool.[27,28,46,55] The extent of tumor resection was calculated, by using pre- and postoperative T2-weighted MR images, on the basis of the methodology described by Smith et al.: (preoperative tumor volume − postoperative tumor volume)/preoperative tumor volume.[56]

For the postoperative volume reconstructions, we used MR images in DICOM format (Digital Imaging and Communications in Medicine) from MRI studies performed 4 months after surgery. Moreover, to evaluate the role of the diffuse tumor growth pattern on postoperative seizure control, the preoperative volumetric difference on T2- and T1-weighted MR images was also assessed, as reported by Skrap et al.: [ΔVT2T1 value = (preoperative tumor volume on segmented T2-weighted images − preoperative tumor volume on segmented T1-weighted images)].[28,55]

Statistical Analysis

Characteristics of the study population are described using mean ± SD or median and range for continuous variables and percentages for categorical variables. For outcome analyses, Engel classification was dichotomized as Class I versus Class II–IV. In other words, patients were classified as either completely seizure free or not completely seizure free.

Data were tested for normal distribution using the Shapiro-Wilk test. The t-test or Mann-Whitney U-test, as appropriate, were used to compare continuous variables between groups. For categorical variables, cross-tabulations were generated, and a chi-square or Fisher's exact test was used to compare distributions, as appropriate. Interobserver reproducibility of preoperative EEG and intraoperative ECoG findings was assessed by the weighted Cohen's kappa. Analyses were tailored to address associations between demographic and surgery-related variables and postoperative seizure control at 12-month follow-up. Univariate analyses were carried out using the chi-square or Fisher's exact test for categorical variables and the t-test or Mann-Whitney U-test for continuous variables. In univariate analysis, the variables considered as possible prognostic factors were age, sex, preoperative tumor volume, tumor histological subtype, tumor side, preoperative seizures features, seizure onset characteristics and frequency, time between seizure onset and surgery, intraoperative protocol used, intraoperative ECoG data, EOR, residual tumor volume, and ΔVT2T1 value. EOR was modeled both as a continuous and an ordinal variable (< 70%, 70%–89%, and ≥ 90%) in univariate analysis, to ensure consistency with previous studies that focused on the impact of glioma resection in terms of volumes.[28,50,55,56] The ΔVT2T1 value and residual tumor volumes were similarly treated as both continuous and ordinal variables. The ΔVT2T1 categories were < 30 cm^3 and ≥ 30 cm^3, while residual tumor volume was subdivided into 4 categories: < 10 cm^3, 10–19 cm^3, 20–29 cm^3, and ≥ 30 cm^3. Preoperative tumor volume was treated as a continuous variable. Multivariate stepwise backward analyses included all variables significant at $p \leq 0.15$ in univariate analysis. For inclusion in the multivariate model, seizure-onset features were dichotomized as "generalized" or "non-generalized," while volumetric parameters were all treated as continuous values. Retention in the stepwise multivariate model required the variable to be significant at $p < 0.05$.[60] Results are presented as odds ratios and 95% confidence intervals. To explore the possible association between ΔVT2T1 values and EOR, preoperative EEG and intraoperative ECoG patterns, the Spearman's rank correlation coefficient was calculated. For clinical purposes, these results are also shown in tables as frequencies and percentages. Furthermore, chi-square or Fisher's exact test, as appropriate, were used to explore a possible association between differences in preoperative tumoral volumes computed on T2- and T1-weighted MR images, ΔVT2T1 value, and EOR achieved. All analyses were conducted with Stata/SE 12.0 for Microsoft Windows. All 2-tailed statistical significance levels were set at $p < 0.05$.

Results

Study Population Characteristics

The baseline demographic and preoperative clinical and radiological characteristics of the study population are described in Table 1. In all cases, preoperative MR images showed a lesion that was hypointense on a T1-weighted MRI sequence obtained without contrast medium and hyperintense on a T2-weighted MRI sequence. Preoperative neurological examination was normal in all cases. Seizure was the onset symptom in all patients. In detail, the most common seizure type was focal seizure with secondary generalization (42.31% of cases). With regard to preoperative seizure frequency, patients were categorized as follows: patients with monthly seizures (1–3 seizures per month; 61.54%), patients with weekly seizures (at least 1 seizure per week, range 1–5 seizures per week; 30.77%), and patients with daily seizures (multiple seizures per day, range 2–10 seizures per day; 7.69%).

All patients were considered affected by drug-resistant tumor-related epilepsy, according to the ILAE definition. At surgery, they were all being treated with AEDs and were not seizure-free, despite having already tried at least 2 AEDs (Table 2).

At the time of surgery, 41 patients were being treated with monotherapy and 11 with polytherapy (Table 2). Overall, the median duration between seizure onset and surgery was 4 months (range 3–20 months).

Preoperative EEG Recordings

The interobserver reliability for preoperative EEG recordings was 97.12% (weighted Cohen's kappa = 0.908, $p < 0.0001$). Preoperative EEG patterns were scored as "normal" in 25 patients, "slow" in 16, and "epileptic" in 11. Of the 25 patients with a "normal" preoperative EEG

TABLE 1: Clinical and demographic characteristics of the study population*

Parameter	Value
no. of patients	52
sex	
female	22 (42.31)
male	30 (57.39)
mean age (yrs)	38.73 ± 11.99
tumor side	
left	36 (69.23)
right	16 (30.77)
median preop T2 tumor vol in cm^3 (range)	75.42 (36–174)
median ΔVT2T1 in cm^3 (range)	15 (1–84)
ΔVT2T1 category	
<30 cm^3	37 (71.15)
≥30 cm^3	15 (28.85)
intraoperative protocol	
awake surgery	40 (76.92)
general anesthesia	12 (23.08)
histological tumor subtype	
fibrillary astrocytoma	32 (61.54)
mixed oligoastrocytoma	11 (21.15)
oligodendroglioma	9 (17.31)
intraoperative ECoG pattern	
N (normal)	25 (48.08)
B (spike bursts)	13 (25.00)
C (continuous spikes)	14 (26.92)
median EOR (range)	87% (28–100%)
EOR category	
≥90%	21 (40.38)
70–89%	23 (44.23)
<70%	8 (15.38)
median postop T2 tumor vol in cm^3 (range)	12 (0–112)
postop tumor vol category	
<10 cm^3	22 (42.31)
10–19 cm^3	16 (30.77)
20–29 cm^3	5 (9.62)
≥30 cm^3	9 (17.31)
postop Engel class	
I	35 (67.31)
II	4 (7.69)
III	8 (15.38)
IV	5 (9.62)

(continued)

TABLE 1: Clinical and demographic characteristics of the study population* ***(continued)***

* Values represent number of cases (%) unless otherwise indicated. The preoperative and postoperative tumor volumes are based on T2-weighted MR images. ΔVT2T1 represents the difference between preoperative tumor volumes on T2- and T1-weighted MR images. Intraoperative ECoG patterns were defined as follows. Type N (normal) was characterized by absence of epileptiform discharges with a background activity depending on the anesthesiological protocol used. Type B (spike bursts) was characterized by the sudden occurrence of spikes for at least 1 second, with a frequency of 10 Hz or more. Type C (continuous spikes) was characterized by spikes occurring rhythmically at regular time intervals for at least 10 seconds, the interval between 2 successive spikes being 1 second at the most.

pattern, 23 (92.0%) had Engel Class I outcomes as assessed at follow-up. Of the 16 patients with a "slow" EEG pattern, 10 (62.5%) had Engel Class I outcomes, while only 2 (18.2%) of the 11 patients with an "epileptic" preoperative EEG pattern had an Engel Class I outcome.

Surgical Procedure and Intraoperative ECoG

Intraoperative electrical stimulation was performed at both the cortical and the subcortical level under general anesthesia in 12 cases and under local anesthesia in 40 cases. Digital intraoperative pre-resection ECoG recording data were reviewed in all cases. In detail, ECoG Pattern N, as previously described, was characterized by the absence of epileptiform discharges, with background activity depending on the anesthesiological protocol. This pattern was observed in 25 patients (48.08%) and all had Engel Class I outcome at the 1-year follow-up evaluation. ECoG Pattern B, was recorded in 13 patients (25%). Nine patients with this pattern during intraoperative ECoG had Engel Class I outcomes. ECoG Pattern C was observed in 14 cases (26.92%). Only 1 patient with this pattern had good seizure control (Engel Class I) at 1-year follow-up.

The interobserver agreement for intraoperative ECoG recordings was 98.56% (weighted Cohen's kappa = 0.961, $p < 0.0001$).

Postoperative Course

In the immediate postoperative phase, a worsening of neurological status was observed in 16 patients (30.76%), as follows. Motor deficits developed in 9 patients (17.3%) (hemiplegia in 1 patient and moderate hemiparesis in 8 patients), while speech disorders occurred in 6 patients (11.5%) (articulatory disorders in 1 patient, phonemic paraphasia without comprehension deficit in 5 patients). At the 3-month follow-up examination, the neurological condition of all but 1 patient had improved and returned to the initial level. There was no statistically significant correlation between side, age, side of the lesion, or extent of resection and postoperative neurological morbidity. The neuropathological examination led to the diagnosis of WHO Grade II glioma in all cases. In detail, the diagnosis was as follows: fibrillary astrocytoma in 32 cases, oligodendroglioma in 9, and mixed oligoastrocytoma in 11.

TABLE 2: Preoperative seizure characteristics*

Parameter	No. of Cases (%)
seizure-onset features	
motor	12 (23.08)
somatosensory	5 (9.62)
vegetative	8 (15.38)
auditory	3 (5.77)
viscerosensory or emotional, incl exp of fear	2 (3.85)
partial w/ secondary generalization	22 (42.31)
seizure frequency	
monthly	32 (61.54)
weekly	16 (30.77)
daily	4 (7.69)
duration	
<1 yr	38 (73.08)
>1 yr	14 (26.92)
AED therapy	
levetiracetam	31 (59.62)
phenytoin	5 (9.62)
carbamazepine	4 (7.69)
polytherapy	12 (23.08)
preop EEG pattern	
N (normal)	25 (48.08)
S (slow)	16 (30.77)
E (epileptic)	11 (21.15)

* Electroencephalogram patterns were defined as follows: Type N (normal) was characterized by a background activity of alpha or faster rhythms, without focal or diffuse slowing; focal and diffuse epileptiform activity (spikes, polyspikes, spike-and-wave and polyspikes-and-wave complexes) was absent. Type S (slow) was characterized by a background of alpha with focal or multifocal theta or delta activity. A wakefulness EEG with background activity of alpha mixed with diffuse theta-delta activity was also classified as "slow." Epileptiform activity was not present. Type E (epileptic) was characterized by a background of alpha, faster rhythms or alpha mixed with slower activities, and localized or diffused epileptic features (spikes, polyspikes, spike-and-wave and polyspikes-and-wave complexes) were recorded. exp = experience; incl = including.

Volumetric Analysis

Data on tumor resection are shown in Table 1. The median preoperative tumor volume, computed on T2-weighted MR images, was 75.42 cm^3 (range 36–174 cm^3); the median preoperative ΔVT2T1 value was 15 cm^3 (range 1–84 cm^3). On the basis of the methodology described by Skrap et al.,[55] the study population was divided into 2 subgroups (Subgroup A [37 cases]: patients with ΔVT2T1 < 30 cm^3; and Subgroup B [15 cases]: patients with ΔVT2T1 ≥ 30 cm^3). Finally, the median residual tumor volume, computed on postoperative T2-weighted MR images, was 12 cm^3 (range 0–112 cm^3). The median extent of tumoral volume resection was 87% (range 28%–100%). Resection of at least 90% of the preoperative tumoral volume was achieved in 21 patients (40.38%), and resection estimated at between 70% and 89% in 23 patients (44.23%). Partial resection (< 70% of the preoperative tumoral volume) was performed in 8 patients (15.38%). Of patients with EOR ≥ 90%, 85.71% became seizure free (Engel Class I), while for patients with EOR ranging from 70% to 89%, this rate was 65.22%. None of the 8 patients with EOR < 70% was completely seizure free 12 months after surgery.

Factors Influencing Postoperative Seizure Control

The postoperative seizure outcome was proportionally similar at the 4 time points (1-, 3-, 6-, and 12-month follow-up).

At 12 months' follow-up, the majority of patients had received some benefit with respect to seizure control. In detail, 67.31% were completely seizure free (Class I), 7.69% had rare seizures (Class II), 15.38% had meaningful improvement (Class III), and 9.62% showed no improvement (Class IV). Overall, 75% of patients achieved satisfactory postoperative seizure control (Engel Class I or II).

Patients with Engel Class II–IV outcome required changes in AED therapy to optimize seizure control after surgery. However, as of the 12-month postoperative follow-up evaluation, those therapeutic changes failed to produce complete seizure freedom, and no other patients achieved Engel Class I.

The univariate analysis showed that the following prognostic factors were associated with complete postoperative seizure control (Engel Class I) ($p < 0.05$): frequency of preoperative seizures; time from seizure onset to surgery; seizure-onset features; preoperative ΔVT2T1 value; preoperative EEG pattern; EOR; intraoperative ECoG pattern; and postoperative residual tumor computed on T2-weighted images. These results are summarized in Table 3. The main factors we found to be associated with seizure outcome were the preoperative ΔVT2T1 value, EOR, and the postoperative residual tumor volume computed on T2-weighted images, treated as both continuous and ordinal variables ($p < 0.0001$). In detail, an increase in the EOR and, consequently, a decrease in the postoperative residual tumor volume as well as a lower preoperative ΔVT2T1 value were associated with better postoperative seizure control (Fig. 1). For graphic visualization purposes, the ΔVT2T1 value was categorized into 2 subgroups (ΔVT2T1 value < 30 cm^3 vs ΔVT2T1 value ≥ 30 cm^3), highlighting a better seizure outcome for patients with a preoperative ΔVT2T1 value < 30 cm^3 ($p < 0.0001$) (Fig. 2). The EOR was divided into 3 categories, and statistical analysis showed that seizure outcome was worse for those patients with an EOR < 70% ($p < 0.0001$) (Fig. 3). To explore the actual role of those factors, a multivariate analysis was performed. The variables that were marginally significant at univariate analysis ($p \leq 0.15$) were entered into a multivariate logistic regression model, excluding those variables with 0% frequencies in some modalities (for example, intraoperative ECoG; Table 3).

In the final model, ΔVT2T1 was shown to be the only variable significantly affecting our outcome; postoperative seizure control was worse in those patients with higher preoperative ΔVT2T1 values (treated as a continuous variable [cm^3]: OR 1.29, 95% CI 1.12–1.50, $p < 0.0001$). Consequently a strong inverse association between EOR

TABLE 3: Univariate predictors of seizure control at 12 months after surgery for insular LGG*

Variable	Engel Class		p Value
	I	II, III, or IV	
age (yrs)	39.39 ± 12.21	37.58 ± 11.85	0.604
sex			0.575
female	13 (39.39)	9 (47.37)	
male	20 (60.61)	10 (52.63)	
tumor side			0.179
right	8 (24.24)	8 (42.11)	
left	25 (75.76)	11 (57.89)	
seizure-onset features			**0.013**
motor	5 (15.15)	7 (36.84)	
somatosensory	3 (9.09)	2 (10.53)	
vegetative	2 (6.06)	6 (31.58)	
auditory	3 (9.09)	0	
viscerosensory or emotional, incl experience of fear	2 (6.06)	0	
generalized	18 (54.55)	4 (21.05)	
seizure frequency			**0.008**
monthly	24 (72.73)	8 (42.11)	
weekly	9 (27.27)	7 (36.84)	
daily	0	4 (21.05)	
duration			**0.002**
<1 yr	29 (87.88)	9 (47.37)	
>1 yr	4 (12.12)	10 (52.63)	
preop EEG pattern			**0.001**
N (normal)	21 (63.64)	4 (21.05)	
S (slow)	10 (30.30)	6 (31.58)	
E (epileptic)	2 (6.06)	9 (47.37)	
mean preop T2 tumor vol (cm^3)	79.06 ± 41.45	69.11 ± 36.18	0.387
mean preop ΔVT2T1 (cm^3)	11.18 ± 5.84	39.47 ± 17.94	**<0.0001**
ΔVT2T1 category			**<0.0001**
<30 cm^3	33 (100)	4 (21.05)	
≥30 cm^3	0	15 (78.95)	
histological tumor subtype			0.277
oligodendroglioma	4 (12.12)	5 (26.32)	
oligoastrocytoma	6 (18.18)	5 (26.32)	
fibrillary astrocytoma	23 (69.70)	9 (47.37)	
intraoperative ECoG pattern			**<0.0001**
N (normal)	25 (75.76)	0	
B (spike bursts)	7 (21.21)	6 (31.58)	
C (continuous spikes)	1 (3.03)	13 (68.42)	
mean EOR (%)	89.94 ± 6.69	71.21 ± 17.14	**<0.0001**
EOR category			**<0.0001**
≥90%	18 (54.55)	3 (15.79)	
70–89%	15 (45.45)	8 (42.11)	
<70%	0	8 (42.11)	
median postop T2 tumor vol (range)	6 (0–34)	23 (4–112)	**<0.0001**
postop tumor vol category			**<0.0001**
<10 cm^3	19 (57.58)	3 (15.79)	
10–19 cm^3	11 (33.33)	5 (26.32)	

(continued)

TABLE 3: Univariate predictors of seizure control at 12 months after surgery for insular LGG* *(continued)*

Variable	Engel Class		p Value
	I	II, III, or IV	
postop tumor vol category *(continued)*			**<0.0001**
20–29 cm^3	2 (6.06)	3 (15.79)	
≥30 cm^3	1 (3.03)	8 (42.11)	

* Bold type indicates statistically significant results ($p < 0.05$).

and ΔVT2T1 was found (Spearman's rank correlation: rho = −0.703, $p < 0.0001$), explaining the lack of association between EOR and better seizure control in our multivariate analysis.

Finally, the present investigation highlighted a significant association between tumor growth pattern and preoperative EEG patterns (Table 4), as well as between tumor growth pattern and intraoperative ECoG patterns (Table 5; Figs. 4 and 5), clarifying why electrophysiological features seem to be associated, on univariate analysis, with better seizure control.

Discussion

Recently, several surgical studies based on the objective evaluation of EOR have been published, suggesting that an extensive surgery leads to increased overall patient survival, decreased malignant progression, and better seizure control.[22–24,27,28,30,37,43] Indeed, LGGs have a clear propensity for the insular lobe, spreading along the intricate network of afferent and efferent connections.[15,16,19] Moreover, due to the surrounding functional and vascular structures, the resection of insular tumors is risky and challenging. Although, maximal resection has recently been demonstrated to be the first therapeutic option in LGG management,[13,14,28,33,37,49,50,52,55,56] less attention has been given to the effect of surgery on tumor-related epilepsy in patients with insular LGGs.

Because surgically treated patients can survive for many years after surgery and quality of life is a critical factor,[24,30] a better understanding of the relationship between tumor-related epilepsy and surgery is needed. There are no universally agreed-upon guidelines to iden-

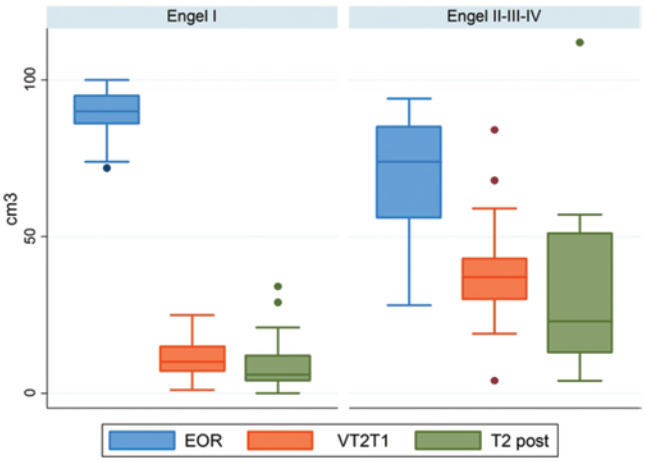

Fig. 1. Box and whiskers plots illustrating the effect of preoperative ΔVT2T1 value *(orange)*, EOR *(blue)*, and postoperative residual tumor computed on T2-weighted images *(green)*, treated as continuous variables, on seizure control (Engel class). An increase in the EOR achieved, and consequently a decrease in the postoperative tumoral residual volume, as well as a lower preoperative ΔVT2T1 value were associated with a better postoperative seizure outcome. The *circles* represent the suspected outliers.

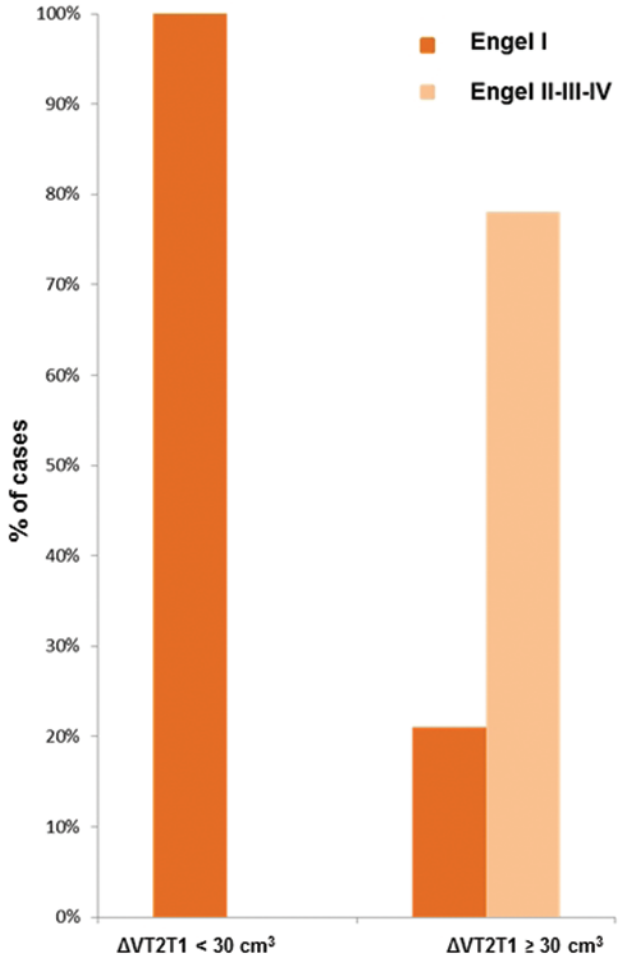

Fig. 2. Graph illustrating 12-month postoperative outcome (Engel class) stratified by preoperative ΔVT2T1 value. A preoperative ΔVT2T1 value ≥ 30 cm^3 indicates the prevalence of the diffusive tumoral growing pattern and was associated with poorer postoperative seizure control ($p < 0.0001$). A major volumetric difference between T2-weighted and contrast-enhanced T1-weighted MRI sequences suggests a greater propensity of the tumor to have a diffuse growing pattern and consequently to be less resectable.

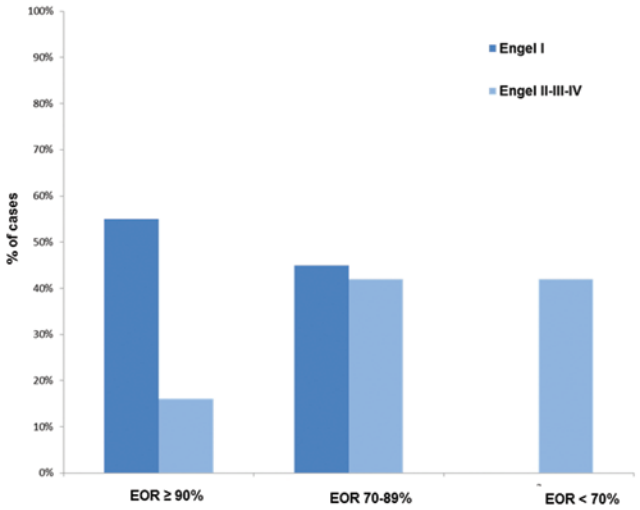

Fig. 3. Graph illustrating seizure control (Engel class) at 12 months after surgery. Seizure outcome was stratified by EOR achieved. The postoperative seizure outcome was better for those patients with an EOR ≥ 90% ($p < 0.0001$).

tify insular LGG patients with a higher risk of developing drug-resistant epilepsy postoperatively. Emerging literature strongly suggests that a greater EOR represents the strongest predictor of seizure control in patients with LGGs.

Zaatreh and colleagues[68] demonstrated a 95% reduction of seizures with subtotal lobectomy, while Duffau et al.[17] showed that 82% of patients were seizure free after "extended lesionectomy" for medically intractable epilepsy caused by insular LGGs. However, even in cases of maximal resection, the percentage of patients who obtain seizure control has been described as ranging from 65% to 80%.[9,13,16,18] Beyond the oncological benefit of extensive resection, these data suggest that the EOR is a strong predictor of postoperative seizure outcome in insular LGGs patients.

To the best of our knowledge, there is no single statistical model that can evaluate the impact of all clinical and neuroradiological variables to identify the risk of postoperative drug-resistant epilepsy in patients undergoing surgery for insular LGG.

Thus, considering the variability reported in literature about postoperative seizure control, in the present investigation, we have specifically applied a statistical model to evaluate the impact of each pre- and postoperative factor on seizure outcome.

Seizure Predictor Factors

Although large studies have evaluated the factors that may predict tumor progression, less is known about what may compromise postoperative seizure control.[13,16,17,19,65] The present investigation is the first to introduce a multivariate analysis to assess the prognostic factors of seizure outcome after insula surgery.

The factors associated with postoperative seizure freedom were a preoperative history of seizures for less than 1 year, preoperative ΔVT2T1 value, preoperative seizure frequency, preoperative EEG pattern, intraoperative ECoG pattern, preoperative ΔVT2T1 value, EOR achieved, and residual volume tumor computed on postoperative T2-weighted images (Table 3).

Our data demonstrated that at last follow-up 87.88% of patients who had had seizures for less than 1 year before surgery were seizure free versus 12.12% of those with a preoperative seizure history of more than 1 year's duration ($p = 0.002$). This result may argue for earlier resection of LGGs associated with seizures, even if they are small and not showing progression.[9,22,57]

Also preoperative seizure frequency was found to be a predictor of postoperative epileptological outcome ($p < 0.008$). In fact, patients with daily seizures before surgery had a worse seizure outcome than those who had monthly seizures, confirming, as extensive experimental investigations have shown, that "seizures beget seizures." In fact, the recurrence of seizures leads to cell loss with the consequent creation of novel excitatory synapses that contribute to the generation of further seizures.[4,63] Early surgery may permit the removal of localized epileptic foci, reducing the occurrence of the phenomenon known as "kindling."[4]

In addition, the present investigation shows that preoperative EEG as well as intraoperative ECoG may be indicators of cortical involvement in epileptogenic networks. Patients in whom preoperative EEG demonstrated epileptic activity and patients with Pattern C on intraoperative ECoG had worse seizure outcome at 1-year follow-up. Conversely, normal activity on preoperative EEG and Pattern N on intraoperative ECoG were statistically associated with postoperative seizure control. Thus, considering the role of the peritumoral environment in tumor-related seizure,[51] these results could suggest the existence of complex epileptic network reorganization in peritumoral tissue itself.

Analysis of the tumor resection data showed a statistically significant association between EOR and seizure outcome, as previously reported by Chang et al.[9] Our data

TABLE 4: Association between preoperative ΔVT2T1 value and preoperative EEG*

Category	Preoperative EEG			
	Pattern N	Pattern S	Pattern E	Total
ΔVT2T1 <30 cm^3	23 (62.16)	12 (32.43)	2 (5.41)	37 (100)
ΔVT2T1 ≥30 cm^3	2 (13.33)	4 (26.67)	9 (60.00)	15 (100)
all cases	25 (48.08)	16 (30.77)	11 (21.15)	52 (100)

* Values represent numbers of cases (%). The association between preoperative ΔVT2T1 value and preoperative EEG pattern was statistically significant ($p < 0.0001$).

TABLE 5: Association between preoperative ΔVT2T1 value and intraoperative ECoG*

Category	Intraoperative ECoG Pattern			
	Normal (N)	Spike Bursts (B)	Continuous Spikes (C)	Total
ΔVT2T1 <30 cm^3	25 (67.57)	11 (29.73)	1 (2.70)	37 (100)
ΔVT2T1 ≥30 cm^3	0 (0.00)	2 (13.33)	13 (86.67)	15 (100)
all cases	25 (48.08)	13 (25.00)	14 (26.92)	52 (100)

* Values represent numbers of cases (%). The association between preoperative ΔVT2T1 value and intraoperative ECoG was statistically significant ($p < 0.0001$).

showed also that the residual tumor volume computed on postoperative T2-weighted images influences seizure outcome ($p < 0.0001$).

Among several factors analyzed in this investigation, particular attention was paid to the volumetric analysis of EOR and the ΔVT2T1 value. The aim was to analyze the roles of resection and peritumoral infiltrated tissue, respectively, with regard to postoperative seizure outcome.

It has recently been demonstrated that the higher the ΔVT2T1 value is, the less extensive is the resection achieved.[28] In fact, we may consider that residual tumor volume represents an indirect index of ΔVT2T1 value. In fact, the EOR is closely associated with the tumor growth pattern (ΔVT2T1), as shown by the Spearman's rank correlation ($r_s = -0.703$, $p < 0.0001$) in this study and as previously demonstrated by Ius et al.[28] Indeed, EOR is inversely related to the tumor growth pattern, which explains why EOR is not associated with better seizure control ($p = 0.387$) in our multivariate analysis; preoperative tumor volume alone is not sufficient to discriminate the compact part of the tumor from the infiltrative part. The biological tumor growth pattern is, in effect, the strongest natural predictor of postoperative seizure outcome.

Furthermore, analyzing in detail the correlation between preoperative ΔVT2T1 value and postoperative seizure outcome, we found that patients with a ΔVT2T1 value of 30 cm^3 or greater ($p < 0.0001$) have worse 1-year postoperative seizure control than those with a ΔVT2T1 value of less than 30 cm^3 ($p < 0.0001$).

Finally, when ΔVT2T1 is removed from our multivariate model, EOR remains as the only strong predictor of better seizure control (OR 0.86, 95% CI 0.78–0.94, $p = 0.001$).

We can conclude that the less infiltrative the tumor growth pattern is, the better are the chances of greater EOR and, consequently, the better is the postsurgical seizure control.

Clinical Role of Peritumoral Infiltrated Tissue

Different mechanisms are believed to be involved in the pathogenesis of tumor-related epilepsy, depending

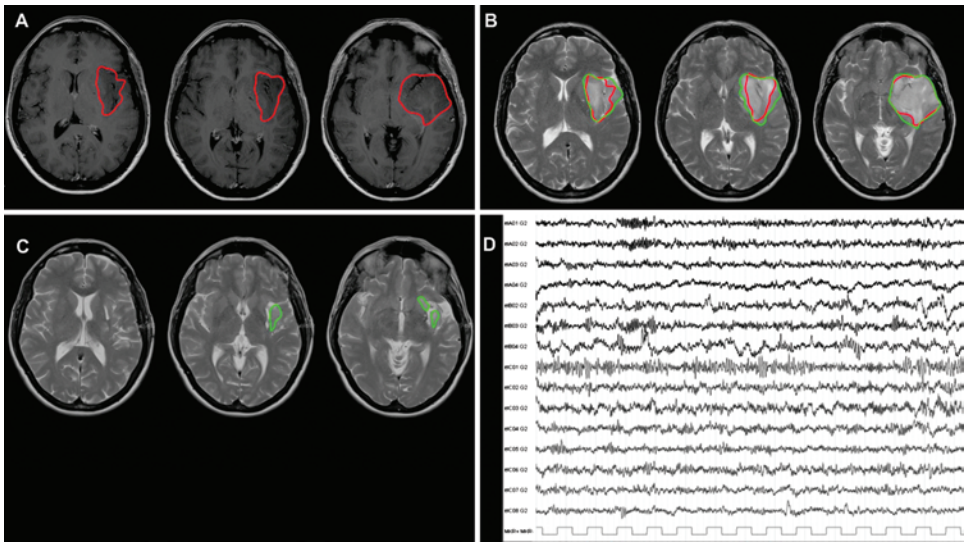

Fig. 4. Axial MR images and ECoG recording obtained in a patient with a left temporal-insular LGG with prevalence of the proliferative tumoral growing pattern (preoperative ΔVT2T1 value < 30 cm^3): the tumor shape is regular, comparable in both postcontrast T1-weighted and T2- weighted MR images. **A:** The preoperative tumoral volume computed on postcontrast T1-weighted MR images was 36 cm^3. **B:** Overlap, on preoperative T2-weighted MRI sequence, of the tumoral region of interest defined on the postcontrast T1-weighted images *(red)* and the T2-weighted images *(green)*. The preoperative tumor volume computed on T2-weighted MR images was 42 cm^3. The preoperative ΔVT2T1 value was 7 cm^3. **C:** The volumetric analysis of residual tumor computed on postoperative T2-weighted MR images showed a residual volume of 1.3 cm^3. The extent of the tumor volume resection, computed on T2-weighted MR images, was 99.4%. **D:** Intraoperative ECoG recording with Pattern N: absence of epileptiform discharges during the surgical procedure.

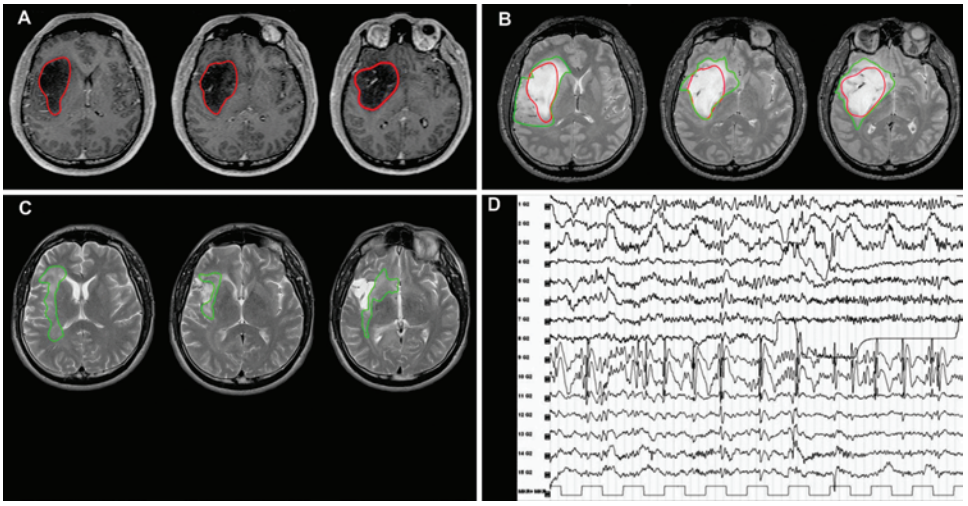

Fig. 5. Axial MR images and ECoG recording obtained in a patient with a right frontal temporal-insular LGG with prevalence of infiltrative tumoral growing pattern (preoperative ΔVT2T1 value ≥ 30 cm^3). The tumor shows digitations along the white matter, resulting in a complex irregular shape more visible on T2-weighted MR images. **A:** The preoperative tumoral volume computed on postcontrast T1-weighted MR images was 88 cm^3. **B:** Overlap, on preoperative T2-weighted MRI sequence, of the tumoral region of interest defined on the postcontrast T1-weighted images *(red)* and the T2-weighted images *(green)*. The preoperative tumor volume computed on T2-weighted MRI sequence was 126 cm^3. The preoperative ΔVT2T1 value was 38 cm^3. **C:** The volumetric analysis of postoperative tumoral residue computed on T2-weighted MR images showed a tumoral residual volume of 38.4 cm^3. The extent of the tumor volume resection, computed on T2-weighted MRI sequence, was 69.5%. **D:** Intraoperative ECoG recording with pattern Type C: presence of spikes occurring rhythmically at regular time intervals for at least 10 seconds over the entire course of the surgical procedure.

on specific tumor histology, integrity of the blood-brain barrier, receptor balance, and characteristics of the peritumoral environment.[22,24,44,47,48,51,57] One of the earliest described mechanisms is the mass effect, with compression of surrounding brain parenchyma causing ischemia, hypoxia, and acidosis, which modify neuron excitability.[1,11,62,66] Recently, more attention has been given to structural changes in peritumoral tissue.[48,51,55,57,62]

Aronica et al. found increased expression of gap-junction channels in the perilesional cortex of patients with LGGs.[2] Furthermore, morphological changes, including aberrant neuron migration in the white matter and pyramidal neurons with fewer inhibitory and more excitatory synapses, have been detected.[46,50]

Indeed, glioma invasion appears to alter the discharge properties of the neighboring neurons, converting them to bursting cells and hence providing "pacemaker" cells that drive networks surrounding the tumor.[31] Finally, it has recently been hypothesized that, during the sprouting of tumor cells in normal tissue, glioma cells react to spatial constraints by releasing a high level of glutamate into the extracellular space,[36] inducing imbalance between inhibitory and excitatory mechanisms, causing excitotoxic neuron cell death, and simultaneously facilitating invasion and migration of tumoral cells.[34,58,59]

Consequently, assuming that the ΔVT2T1 value represents the infiltrative component of the tumor, it could be an indirect index of changes in peritumoral tissue induced by tumor growth itself and thus potentially a measure of the development of epileptic networks.

Finally, the main relevance of this study is represented by the objective evaluation of the infiltrative tumor component, expressed by the ΔVT2T1 value. This value may constitute a new predictive index allowing for the preoperative identification of patients with higher risk of postoperative drug-resistant epilepsy, due to limitations on the achievable EOR.

Nonetheless, our study has some limitations. First, it is retrospective, and this methodology does not allow a standardized follow-up. Other limitations of the present investigation include the limited number of cases analyzed in univariate and in multivariate analysis, as well as the short follow-up period. Finally, molecular markers, which are increasingly used for the assessment and management of LGG, were not included in the statistical analysis due to their recent introduction in clinical practice.[8] Ongoing and future randomized trials of LGG treatment will offer the opportunity to reveal the possible relationships between the molecular profiles and seizure outcome, detecting the histological subtypes more likely to result in drug-resistant epilepsy.

Conclusions

The present investigation confirms the role of EOR in postoperative seizure outcome in insular LGGS. It highlights that the EOR itself depends on the level of the infiltrative tumoral growing pattern expressed by the preoperative ΔVT2T1 value.

The higher is this value preoperatively, the lower is the chance for a better postoperative seizure control, as a consequence of minor tumoral resection achieved.

The individual evaluation of the prevalent tumoral pattern, by means of preoperative neuroimaging, represents a helpful tool to identify patients with an increased risk of major postoperative residual tumor and consequent seizure persistence after surgery.

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Disclosure

The authors attest that they have no personal financial or institutional interest in any of the drugs, materials, or devices described in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Ius, Skrap. Acquisition of data: Ius. Analysis and interpretation of data: Ius, Pauletto, Isola. Drafting the article: Ius, Pauletto. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Ius. Statistical analysis: Ius, Isola, Gregoraci. Administrative/technical/material support: Ius. Study supervision: Ius, Skrap.

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