NEUROLOGY INDIA

Publication of the Neurological Society of India

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ORIGINAL ARTICLE

Year: 2023 | Volume: 71 | Issue: 4 | Page: 682--688

Postoperative Seizure Control in Adult Diffuse Insular Gliomas Presenting with Seizures: A Retrospective Single-Center Experience and Proposal of a Novel Risk Scoring System

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Abstract

Background: Studies on insular gliomas (IGs) generally focus on the oncological endpoints with a relative scarcity of literature focusing on the seizure outcomes. **Objectives:** To study the predictors of long-term postoperative seizure control in IG and propose a novel risk scoring system. **Methods:** Histopathologically proven, newly diagnosed adult IGs (>18 years) operated over a 10-year period were studied for postoperative seizure control as per International League Against Epilepsy (ILAE) grades at 6 weeks and at last follow-up (minimum of 6 months, median 27 months). Logistic regression analysis was performed and regression coefficients with nearest integers were used to build a risk prediction model. Receiver operator curve (ROC) analysis determined the predictive accuracy of this model. **Results:** The 6-week postoperative seizure freedom dropped to 41% at the last follow-up. The seizure-free group lived longer (100.69 months, 95% CI = 84.3–116.99 (60%)) than those with persistent postoperative seizures (27.92 months, 95% CI = 14.99–40.86). Statistically significant predictors (preoperative seizure control status, extent of resection, tumor extension to temporal lobe, and lack of postoperative adjuvant therapy) were used to compute a risk score, the score ranging from 0 to 9. A score of four most optimally distinguished the risk of postoperative seizures with an area under the ROC of 91.4% (95% CI: 84.1%, 98.7%, *P* < 0.001). **Conclusion:** In our experience, around 60% of patients obtained seizure freedom after surgery, which reduces over time. Control of seizures paralleled survival outcomes. Our proposed scoring system may help tailor management strategies for these patients.

How to cite this article:

Das KK, Singh A, Mishra P, Khatri D, Deivasigamani BK, Datta A, Bhaisora KS, Mehrotra A, Srivastava AK, Jaiswal AK, Behari S, Kumar R. Postoperative Seizure Control in Adult Diffuse Insular Gliomas Presenting with Seizures: A Retrospective Single-Center Experience and Proposal of a Novel Risk Scoring System.Neurol India 2023;71:682-688

How to cite this URL:

Das KK, Singh A, Mishra P, Khatri D, Deivasigamani BK, Datta A, Bhaisora KS, Mehrotra A, Srivastava AK, Jaiswal AK, Behari S, Kumar R. Postoperative Seizure Control in Adult Diffuse Insular Gliomas Presenting with Seizures: A Retrospective Single-Center Experience and Proposal of a Novel Risk Scoring System. Neurol India [serial online] 2023 [cited 2023 Sep 10];71:682-688 Available from: https://www.neurologyindia.com/text.asp?2023/71/4/682/383844

Full Text

Insular gliomas (IGs) are challenging neurosurgical conditions.[1] Ever since Prof. Yasargil published his seminal work[2], numerous papers have established the safety and efficacy of aggressive insular glioma surgery.[1],[3],[4],[5],[6] The lion's share of publications; however, focus on the surgical results and oncological aspects of this disease.[3],[4],[6] Seizures associated with insular glioma have managed to draw neurosurgeon's attention less frequently.[7]

Around 15% of patients with IG develop drug-resistant epilepsy (DRE) and a variable proportion of these patients derive seizure freedom after surgery.[8],[9],[10] Long-standing preoperative seizures, diffuse tumor margins, and residual tumors are known to increase the risk of postoperative seizure persistence.[11],[12],[13] The extent of tumor resection has been proposed to be a major modifiable factor by Wang et al.[7] showing a resection threshold of 80% for the same. It is also

apparent now that recurrence or worsening of seizures correlates with radiological tumor progression.[7],[14]

Therefore, it is imperative to know about postoperative seizure freedom rates, their dynamics with disease progression, and a possible risk stratification tool. Such a system may not only allow symptom-specific disease prognostication but also help in clinical decision making vis-à-vis antiepileptic drug (AED) modification or repeat treatment.

Methods

Patient and tumor evaluation

We included all adult patients (18 years and above) with histopathologically proven, newly diagnosed IG with a history of preoperative seizures operated on over a 10-year period. We excluded those who did not have all the relevant details pertaining to pre- and postoperative seizures, or those with less than 6 months of postoperative follow-up. This study was approved by our institute's ethical committee.

Those who continued to have seizures despite being on AED were considered to have medically uncontrolled seizures as previously published by Wang et al.[7] This definition is different from that proposed by International League Against Epilepsy (ILAE) for DRE as we aimed to study seizures in IGs in general and not DRE specifically. These patients were on various combinations of antiepileptic medications. The medications were continued after hospital admission as well as in the postoperative period.

The extent of resection (EOR) was determined based on the postoperative magnetic resonance imaging (MRI) obtained either within 2–3 days or after 4 weeks of surgery.[15] It was graded as total (no residual tumor), near-total (>90% resection), and subtotal (<90%) tumor resection. We did not use tumor volumetry for this purpose. Surgical complications were either minor or major. While wound complications, small surgical bed hematoma not requiring active intervention were included as minor complications, postoperative neurological deficits comprised major complications in our series. Major complications were again graded as transient and permanent depending on the improvement or persistence of deficit beyond the 3-month time period after surgery.

Follow-up and seizure outcome

Patients were followed up at 6 weeks after surgery and regularly thereafter (3–6 months intervals). Postoperative adjuvant therapy was advised for patients with subtotal resection and all high-grade gliomas. Follow-up records were reviewed at each visit to find out seizure control status as per the ILAE seizure outcome scale.[16] For this study, we divided seizure control into the following two types: good seizure control (grades 1 and 1a) and poor seizure control (grades 2–6). Seizure outcome at 6 weeks and at last follow-up was recorded.

Survival analysis

Time from surgery till death was considered as overall survival (OS) and expressed in months. Kaplan–Meier's method was used to calculate survival. Seizure outcome at follow-up was correlated with OS using the Log-rank test.

Statistical analysis and development of risk stratification score

A variable was considered normally distributed when skewness was within ± 2 . Independent samples t-test/Mann–Whitney U test was used to compare the continuous distribution between controlled and uncontrolled seizures groups. The Chi-square test was used to test the association between patient outcomes and demographic/clinical variables.

Univariate analysis was used to identify the variables associated with unfavorable postoperative seizure outcomes. These included: demographic variables (patient age [<40 vs. >40], gender), clinical variables (preoperative seizure type, duration of symptoms, the status of preoperative seizure control [controlled vs. uncontrolled], number of ongoing preoperative antiepileptic drugs [1 vs. >1]), radiological variables (Berger-Sanai Zones involved, side of the tumor, the extension of the tumor, tumor border on MRI, basal ganglia involvement, tumor enhancement), histopathological variables (WHO grade, IDH mutation status), treatment variables (EOR, additional temporal lobe resection, the status of adjuvant therapy [received or not]), and cytoreductive role of surgery on postoperative seizure (seizure control status at 6 weeks after surgery).

The regression coefficients (β) (validated by its 95% CI using Bias-corrected and accelerated [B Ca] in Boot-strapping methods) and adjusted odds ratio were calculated through multivariate analyses. The nearest integers of calculated regression coefficients were taken for the scoring system. The discrimination capability of the risk score and its appropriate cut-off value were assessed through the receiver operating characteristic (ROC) curve with corresponding sensitivity and specificity. Hosmer–Lemeshow test was used to assess the goodness of fit of the model. P value < 0.05 was considered

statistically significant. Statistical package for social sciences, version-23 (SPSS, IBM, Chicago, IL), and Med Calc software were used for data analysis.

Results	

[Table 1] and [Table 2] show the basic patient-related, seizure and treatment characteristics in our study group.{Table 1}{Table 2}

Surgical results

Thirty-one patients (55.4%) underwent a gross total or a near-total tumor resection. A total of 44.6% of patients (n = 25) underwent additional resection of the peritumoral temporal lobe and mesial temporal structures. Seven patients (12.5%) underwent resurgery of which six surgeries were directed at the previous surgical site (3 for residual/recurrent tumor excision, 3 for postoperative hematoma/edema decompression). All three patients with a repeat tumor resection had uncontrolled seizures after a second surgery.

Postoperative major complications were noted in 10 patients (17.8%). Among minor complications, five patients had transient neurological deficits (improved within 3 months of surgery), five patients developed surgical site hematoma, which was managed conservatively in all, and three patients had cerebrospinal fluid (CSF) leak from the wound site, which was also addressed conservatively.

Follow-up results

The median follow-up duration was 27 months (range: 6–99 months). Forty-two of the 56 patients were alive while 14 patients had died (25%). The mean overall survival in our patient cohort was 97.4 months (95% CI = 81.8-113.04). Although it did not reach significant levels statistically, those who were seizure-free lived longer (100.69 months, 95% CI = 84.3-116.99) than those who still had seizures (27.92 months, 95% CI = 14.99-40.86).

Seizure outcome, risk factors, and prediction model for poor postoperative seizure control

Although 59% of the patients were free of seizures at 6 weeks following surgery, the rate of seizure-free status dropped to 41% at a median follow-up of 27 months. Of note, 12 of 33 patients with preoperatively controlled seizures had seizure reappearance despite medications in the long-term follow-up. Clinically, eight patients showed a progressive disease course after the beginning of the postoperative seizures in this group while four patients remained stable with the addition of new AEDs. Neuroimaging eight of these patients was performed around the time of seizure recurrence. While the disease showed progression in six patients, the other two patients had cystic degeneration in the residual tumor without an increase in the tumor mass. [Table 2] shows the findings of the univariate analysis. The factors significant on multivariate analysis were used to generate a risk scoring system [Table 3]. The total score ranged from 0 to 9. There were three patients (5.4%) each who had scores 0 and 5, respectively. Similarly, 12 patients each (12% each) had scores 2, 4, and 7, respectively. [Figure 1] shows the proportional postoperative seizure control rates with different scores.{Table 3}{Figure 1}

Accuracy of the scoring system

We determined the diagnostic accuracy of the risk score at different cut-off values. We found that a score of \geq 4 most optimally distinguished the risk with the best sensitivity (78.8%), specificity (87%), and overall accuracy (82.17%) among the different cut-off scores tested (\geq 3, \geq 5, \geq 6). Area under the ROC (AUROC) curve indicated that the accuracy of the scoring system was 91.4% (95% CI: 84.1%, 98.7%, P < 0.001), indicating an excellent performance of the model [Figure 2]. The Hosmer–Lemeshow goodness of fit test demonstrated a good agreement (82.1%) between predicted and observed poor postoperative seizure (P = 0.925), indicating that there was no departure from a perfect fit.{Figure 2}

Discussion

IGs present a formidable surgical challenge to neurosurgeons. Despite these limitations, recent studies have shown the safety, feasibility, and oncological advantages of aggressive surgical resection in IGs.[1],[3],[4],[5],[6] Thus, modern treatment strategies in IG have translated into oftentimes long survival times and hence the issue of quality of life has assumed a great significance.

Insula has inherent epileptogenic potential, owing primarily to its structure and connections.[1],[2],[9] Around 15% of

patients with insular glioma have intractable seizures.[8] Similar to the finding of Ius et al.,[17] we found that uncontrolled preoperative seizures portended poor postoperative seizure freedom. This underscores the phenomenon of kindling or the "seizure begets seizures" concept. This also underscores the need for early surgery in IGs.

Englot et al.[18] noted that gross total tumor resection, well-controlled preoperative seizures, shorter duration of seizures (<1 year), and nonsimple partial seizure semiology predicted postoperative seizure freedom. Xu et al.[19] showed that a resection threshold of 80% predicted postoperative seizure freedom in supratentorial low-grade gliomas could be considered a "soft target" intraoperatively. As for IGs specifically, Ius et al.[17] reported persistent seizures despite two to three AEDs in all their patients. We also noted that 37.5% of patients had poorly controlled preoperative seizures, although tumor size and related concerns often lead to expeditious surgical excision before the development of DRE in supratentorial gliomas.[18] Previous studies have shown postoperative seizure control in the range of 65%–82%.[7],[17] The seizure control rate reported by Duffau group with an "extended lesionectomy" approach was 82%.[8] Ius et al.[17] showed that peritumoral infiltrated tissue (expressed as the difference in the tumor volumes on T2 and T1 WI, \triangle VT2T1) was the most important adverse factor for postoperative seizure control. Recently, Wang et al.[7] reported 68% seizure freedom 1 year after surgery, which dropped to 39% at the last follow-up. They found that a resection threshold of 80% existed for IGs as well. Interestingly, they noted that seizure worsening preceded radiological tumor progression by 3 months, a finding which we also noted in our study. Interestingly, all our patients with a repeat surgical tumor resection had uncontrolled seizures after the first surgery.

Our univariate analysis revealed certain new risk factors, confirmed a few, which are well known and refuted some. It validated certain factors like uncontrolled preoperative seizures, history of multiple AEDs preoperatively, lack of adjuvant therapy, and subtotal tumor resection. While the first two factors indicate the development of widespread epileptogenic networks, the suboptimal oncological benefit associated with the latter two factors explains seizure persistence. Achieving an optimal EOR in IGs is sometimes challenging due to a combination of Middle Cerebral Artery (MCA) anatomy, corticosubcortical eloquence, and tumor characteristics.[4],[5],[6],[20],[21],[22],[23] Looking at the impact of adjuvant therapy in the seizure control in our study, consideration may be given to adjuvant therapies, particularly chemotherapy, for optimal oncological-seizure control even in maximally resected insular low-grade gliomas.

Our study refuted one well-known favorable prognostic factor, i.e., a lesionectomy plus approach proposed by Duffau et al.[8] We additionally found some relatively lesser-known factors, which included temporal tumor extension, high-grade tumors, and early postoperative seizures as risk factors for postoperative seizure freedom. A temporal extension may indicate more widespread recruitment of abnormal circuitry and kindling of mesial temporal structures that affect seizure freedom. Moreover, these tumors could be biologically more aggressive vis-a-vis frontally extending tumors as noted by Simon et al.[24] We found a novel finding that uncontrolled seizure at first follow-up (6 weeks) portended a risk for lack of eventual seizure control. While the 6-week time point is a rather very short follow-up point for evaluating a symptom like a seizure, it has the advantage of assessing the cytoreductive role of surgery, before the adjuvant treatment is initiated. Once the adjuvant therapy is administered, it becomes difficult to know, which of the oncological therapies caused seizure control status is determined after some time has elapsed after surgery. No other previous studies have examined the value of early postoperative seizure control status in the eventual seizure control. As our results show, this could be a better judge of the role of EOR on seizure control and this could be used as a prognostic sign for the eventual seizure outcome.

We propose here a risk prediction scoring system for the first time. This score was based on the findings of multivariate analysis of the eight variables found significant in univariate analysis. The other variables, including tumor histopathological grade, did not impact postoperative seizure freedom in the presence of other variables. Ius et al.[17] had previously proposed a model based on multivariate analysis. However, a risk scoring system did not exist previously. We found that an increased risk score correlated with the heightened risk of persistent postoperative seizure. Although a score of two is associated with 8.3% risk, a score of nine has a 100% likelihood of persistent seizures. The significance of preoperative uncontrolled seizures is evident in the final scoring system where this variable itself has a score of 3. However, as our scoring system showed, preoperative seizure (score 3) in itself, does not have the required sensitivity, specificity, and predictive value. A score of 4, which means the additional presence of one more factor, is needed for the same. Thus, the scoring system considers all the risk factors and justifies itself. Therefore, this scoring system considers the multiple factors contributing to postoperative seizure freedom in these patients and provides a real-world estimation of such risks in clinical practice. Prospective validation of our scoring system will be needed to explore the clinical applicability of this score.

Limitations

The findings of our study must be interpreted in the context of certain limitations. A retrospective study design with attendant recall bias, lack of seizure evaluation as per epilepsy protocol, lack of tumor volumetry, and comprehensive molecular characterization of the tumors remain important limitations. Also, the retrospective nature of the study precluded documentation of seizure control data at specific follow-up time points like 6 months, 1 year, and 2 years postoperatively, which reduce the significance of our conclusions to an extent. These limitations notwithstanding, our experience is relatively large as a single institution study, and a long-term follow-up and seizure outcome endpoint set beyond 6 months were also

important strengths of this study. Importantly, we propose a risk scoring system for the first time, which can be utilized to estimate postoperative risk for uncontrolled seizures and allow prognostication.

Conclusions

Modern oncological therapies in IG lead to optimal seizure control in nearly 60% of patients, which tends to reduce with increasing follow-up. Control of seizures adds to the quality of life and translates to better survival outcomes. Our proposed scoring system has high sensitivity and specificity in predicting the risk of persistent postoperative seizures and hence may help tailor management strategies for these patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Table 1: Baseline characteristics of insular glioma with seizures in this series (n=56)

Variable	Frequency	Percentage
Age	Mean	
	35.70 years±22.4	
<40	Range: 18-68	66.1
>/=40	37	33.9
	19	
Gender		
Male	34	60.7
Female	22	39.3
Preop duration	Mean 11.65	
	months±26.4	
<12 months	Range: 1-60	64.3
>/=12 months	36	35.7
	20	
Type of seizure		
SPS	17	30.4
CPS + GTCS	39	69.6
Preop seizures		
Controlled	35	62.5
Not controlled	21	37.5
Preop AED		
1	35	62.5
>/=1	21	37.5
Side		
Right	34	60.7
Left	22	39.3
Enhancement		
Enhancing	17	30.4
Nonenhancing	39	69.6
Tumor extension		
Insular with temporal extension	41	73.2
Insular without temporal extension	15	26.8
Berger Sanai zones	15	20.0
Giant (LIL III IV)	20	35.7
Segmental	20	64.2
J	1	04.0
1	1	
II IV	3	
	1	
1+11	4	
11+111	5	
1+11+111	9	
11+111+1V	13	
Basal ganglia involvement		
Yes	20	35.7

No	36	64.3
Anesthesia type		
GA	49	87.5
Awake	7	12.5
Surgical approach		
Transcortical	26	46.4
Trans-sylvian	30	53.6
Extent of resection		
GTR/NTR	31	55.4
STR	25	44.6
Additional temporal resection		
Yes	25	44.6
No	31`	55.4
Postop complications		
Neurological	17	30.4
Non-neurological	8	14.3
Adjuvant therapy		
Yes	19	33.9
No	37	66.1
Histology		
Grade 2	49	87.5
Grade 3, 4	7	12.5
Туре		
Oligo	8	14.3
Nonoligo	48	85.7
IDH		
Positive	18	32.1
Negative	4	7.1
Not done	34	60.7
Resurgery		
Yes	7	12.5
No	49	87.5
Immediate postop seizure outcome		
No seizure (1a)	33	58.9
Residual seizure (1b-4)	23	41.1
Final postop seizure		
outcome (median follow-up=27		
months)	23	41.1
No seizure (1a)	33	58.9
Residual seizure (1b-4)	87 V.	1912

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Table 2: Univariate analysis of the factors determining postoperative seizure freedom

Variable	Seizure cor follow-up follow-up=2	P Fisher's exact test	
	ILAE grade	ILAE grade	
Age	1112 (11-20)	>14 (11-00)	
<40	16	21	0.77
>/=40	7	12	
Gender			
Male	21	13	0.781
Female	12	10	
Preoperative seizure type			
SPS	6	11	0.76
CPS/GTCS	17	22	
BS zones involved			
Giant	7	13	0.58
Nongiant	16	20	
Duration (months)			
<12	15	21	1.00
>/=12	8	12	
Preoperative seizures:			
Medically controlled	21	12	< 0.001
Medically uncontrolled	2	21	
,,			
Preoperative AED			
1 AED	23	12	< 0.001
>/=1 AED	0	21	
Side of tumor			
Right	13	21	0.78
Left	10	12	
Extension			
Temporal	12	29	0.005
Without temporal	11	4	
Basal Ganglia Involvement			
Yes	6	14	0.26
No	17	19	
Enhancement			
Enhancing	9	8	0.25
Nonenhancing	14	25	
Surgery approach			
Transcortical	12	14	0.59
Trans-sylvian	11	19	
Additional temporal lobe	22.02	0.85740	
resection	5	20	0.006

Yes	18	13	
No			
EOR			
GTR/NTR	18	13	0.006
STR	5	20	
Histology			
High grade	0	7	0.03
Low grade	23	26	
IDH status			
Positive	8	10	0.92
Negative	2	2	
Not done	13	21	
Adjuvant therapy			
Yes	12	7	0.02
No	11	26	
Early postop seizure			
status (6 weeks)	23	10	<0.001
Controlled	0	23	
Uncontrolled			

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Table 3: Proposed risk scoring system (n=56)

Variable	Regression Coefficient (β)		Р	Final Score	Adjusted Odds Ratio	
	Value	BCa 95% Cl			Value	95% CI
Preoperatively medically uncontrolled seizure	2.77	1.11, 39.06	0.002	3	15.99	2.55-100.33
STR	1.97	0.33, 37.44	0.010	2	7.14	1.24-41.14
Tumor extension to temporal lobe	2.08	0.02, 38.70	0.024	2	7.99	1.12-56.83
Lack of postoperative adjuvant therapy	1.83	0.19, 34.24	0.017	2	6.21	1.07-36.20

BCa 95% CI=Bias-corrected and accelerated (BCa) 95% confidence interval. Bootstrap results are based on 1000 bootstrap samples. Multivariate binary logistic regression analysis was used. *P*<0.05 significant

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