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Post-operative Seizure Control in Patients with Tumour Associated Epilepsy

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Abstract

Objective

The patterns of post-operative seizure control and response to anti-epileptic drugs (AED) in tumour associated epilepsy (TAE) are poorly understood. We aim to document these characteristics in patients with supratentorial gliomas.

Methods

This was a retrospective analysis of 186 patients with supratentorial gliomas. Seizure patterns were classified into 4 groups: A - no post-operative seizure; B – early post-operative seizure control within 6 months; C - fluctuating seizure control; D – never seizure-free. Rates and duration of seizure freedom, subsequent seizure relapse and response to AED were analysed.

Results

Among patients included, 49 had (26.3%) grade II, 28 (15.1%) had grade III and 109 (58.6%) had grade IV glioma. Outcome pattern A was observed in 95 (51.1%), B in 22 (11.8%), C in 45 (24.2%) and D in 24 (12.9%). 119 patients had at least one seizure and were classified as having TAE. Compared to pattern A,

pattern B was predicted by histological progression; pattern C by tumour grade, pre-operative seizure and histological progression, and pattern D by pre-operative seizure and gross total resection. Among patients with TAE, 57.5% of grade II, 68.2% of grade III and 26.3% of grade IV experienced a period of 12-month seizure freedom. After first 12-month seizure remission, 39.1%, 60.0%, 13.3% of grade II, III, IV gliomas respectively experienced subsequent seizure. 22.6% of those with TAE reached terminal seizure freedom of at least 12 months on their first post-operative AED regimen, 6.5% on their second regimen and 5.4% on subsequent regimens.

Significance

Distinct patterns of post-operative seizure control exist in gliomas, they have specific risk factor profiles and we hypothesize these correspond to unique pathogenic mechanisms. 12-month seizure freedom with subsequent relapse is frequent in grade II-III gliomas. Response to AEDs is markedly poorer than with non-TAE, highlighting the complex epileptogenicity of gliomas.

INTRODUCTION

Seizures are commonly a presenting feature of supratentorial gliomas[1; 2]. These patients often continue to have seizures after glioma resection, while some only start to experience seizures following surgery[3-6]. The patterns of post-operative seizure control are poorly understood. Previous studies have tended to dichotomise outcomes into seizure freedom and 'uncontrolled' seizures based on cross-sectional analysis [3; 6; 7]. However, seizure control is dynamic and these outcomes represent just two ends of its broad spectrum. While fluctuating control is recognised in the setting of tumour progression and adjuvant therapy[5;

[8-11], its incidence, the duration of remissions and timing of relapses are poorly understood.

The conventional approach to antiepileptic drug (AED) management in tumour associated epilepsy (TAE) is based almost entirely on non-glioma data with only a paucity of evidence derived from trials specifically enrolling patients with TAE[12; 13]. A better understanding of treatment response patterns for TAE is essential for the formulation of rational treatment strategies, including timing of withdrawal of AED therapy, and discussions of lifestyle issues such as fitness to drive. It is vital in the design of prospective treatment trials and may also shed new insights into the neurobiology of this important comorbidity of brain tumours.

To address these issues we retrospectively analysed the post-operative seizure control and treatment response of 186 patients with grade II-IV supratentorial gliomas. We also sought to identify clinicopathological and treatment factors that may predict distinct patterns of seizure outcome.

MATERIALS AND METHODS

Patient selection

We identified subjects from a database of 221 consecutive patients who had oncological surgery between 1988 and 2011 under care of the Department of Neurosurgery, The Royal Melbourne Hospital, following a radiological diagnosis of a supratentorial glioma. The department provides neurosurgical care to adults (≥18 years) primarily living in Melbourne and the State of Victoria, Australia. Patients were included if they had histopathological diagnosis of WHO grade II, III or IV glioma located supratentorially. Histological grading was determined by a single anatomical neuropathologist and was based upon the WHO classification of Tumours of the Central Nervous System[14; 15]. Patients were excluded if only a biopsy was performed, seizures only occurred in the first week after resection or

if less than one month of post-operative seizure control data was available (including if survival was less than 30 days).

Epilepsy treatment

TAE was diagnosed after the first seizure attributable to the glioma[16] and AED was subsequently commenced. Pre-operatively, most patients without seizure were also prescribed AED therapy as prophylaxis by the treating neurosurgeon. Post-operatively, all patients were followed by either a neurosurgeon and/or medical oncologist who undertook initial epilepsy management, with referral to epileptologist if the epilepsy proved difficult to control. As a standard approach, patients were initially treated with single AED. Dose adjustment and drug changes were made based on clinical response in terms of seizure control and adverse effects. Serum AED levels were monitored as clinically indicated. Prophylactic AED was generally ceased after a period of 3-6 months of seizure freedom post-operatively.

Clinico-pathological Data Collection

Clinical information was retrieved from medical records and the Australian Cancer Grid database as part of the BioGrid Australia™ clinical informatics system[17]. Clinicopathological data consisted of gender, age at diagnosis, histopathological diagnosis, side and lobe of lesion. Treatment information included extent of initial surgical resection, and chemotherapy or radiotherapy given at any stage post-operatively. Extent of resection was categorised as gross macroscopic resection, subtotal resection (50-95% tumour excision), partial resection (<50% tumour excision) or biopsy, as determined by post-operative MRI. To account for tumour progression, histological progression on re-resection was recorded; this was defined as an increased glioma grade or recurrence of grade IV glioma.

Pre-operative seizures were defined as seizures attributable to the glioma, occurring before the patient's first surgery. Post-operative seizure control was measured at the following post-operative time intervals: 0-6 months, 6-12 months, 12-18 months, 18-24 months and then yearly thereafter. AED use was

documented over these respective time intervals. The number of AED regimens used by each patient in the post-operative period was recorded. A regimen was defined as the use of a single drug or a combination of two or more[18]. Persistent post-operative seizures despite an adequate trial of two or more appropriate antiepileptic drugs were classified as drug-resistant[19].

Patients were followed up until: i) death, ii) referral to a palliative care service and discharge from surgical/oncological follow-up, iii) lost to follow-up or iv) July 2014, whichever occurred first. Overall survival was defined as time from initial histological diagnosis until last follow-up.

Epilepsy Patterns

Seizure control for each patient was categorised into one of four distinct patterns. Pattern A applies to patients who did not have any post-operative seizures. In pattern B (early seizure control), the seizures occurred only in the first six months post-operatively and the patient became seizure free thereafter. In pattern C, seizure control fluctuated with seizures interspersed with period(s) of seizure remission lasting at least 6 months from 0-24 months post-operatively and then lasting at least 12 months from 24 months post-operatively. In pattern D, the patient never became seizure-free. 'Never seizure free' was defined as having at least 6 monthly seizures from 0-24 months post-operatively and at least yearly seizures thereafter.

Given the possible pathophysiological differences between pre- and post-operative seizures, we performed subgroup analysis on the basis of pre-operative seizure status.

For the patients with TAE, 12 month seizure freedom periods, duration of seizure freedom and time to relapse after 12-month seizure freedom were measured. 'Terminal seizure freedom' was ascertained for each TAE patient with at least 12 months survival, and defined as seizure freedom for at least 12 months at the last follow-up.

Statistical Analysis

The association between clinicopathological variables and seizure control patterns was examined using chi-square test, Fisher exact test, one-way ANOVA and Kruskall-Wallis univariate analyses as appropriate. Variables with $p < 0.05$ on univariate analysis were included in multivariate analysis using manual stepwise multinomial logistic regression. Following Bonferroni correction, age less than 45, gross total resection, histological progression and chemotherapy were considered significant if $p < 0.025$ and all other variables if $p < 0.05$ on multivariate analysis. To make the results more translational for clinicians, age less than 45 years at diagnosis was used instead of a continuous age variable and gross total resection (yes or no) was used rather than multiple 'extent of surgery' variables. Multicollinearity was assessed in variables included in multiple regression analysis and was indicated by a variable inflation factor (VIF) greater than 3.0. Kaplan-Meier analyses were utilised to estimate cumulative probability of entering terminal seizure freedom according to the number of AED regimens trialed. A log-rank test was employed to compare all Kaplan-Meier survival curves. Missing data were considered a specific category in all analyses. All analyses were performed with SPSS - version 22 (SPSS Inc., Chicago, IL).

Ethics

This study protocol was approved by the Melbourne Health Human Research and Ethics Committee (HREC 2006.199).

RESULTS

Patient cohort

Of the 221 subjects in our database, one patient with a cerebellar tumour, one with ependymoma, 17 with biopsy only, 9 with less than 30 days of follow-up data and 7 patients with seizures only in the first post-operative week were excluded. The remaining 186 subjects were included in the analysis (Table 1).

Patients were followed up for a median of 16.9 months overall (IQR 9.0 – 57.2 months). Grade II gliomas had a follow-up of 62.1 months (IQR 38.6 – 91.9 months); Grade III gliomas 44.6 months (IQR 15.4 – 96.3 months); Grade IV

gliomas 11.0 months (IQR 4.6 – 17.2 months). Grade IV glioma patients who received adjuvant chemoradiotherapy (n=83) had a median survival of 14.5 months (IQR: 9.8 – 22.7 months).

Pre-operative seizures were experienced by 81 (43.5%). Thirty-eight (20.4%) patients without pre-operative seizures had seizures after surgery. Hence a total of 119 (64.0%) patients who experienced either pre-operative seizures or at least one post-operative seizure were diagnosed as having tumour associated epilepsy.

Only 1 patient without a pre-operative seizure did not receive prophylactic AED and this patient did not have any post-operative seizures. AED were withdrawn in 22 of 186 patients post-operatively and 5 had a subsequent seizure; all five had had a pre-operative seizure. Therefore, in total, five of 186 patients had post-operative seizures while not taking AED.

Phenytoin was used in 140 (78.7%) patients, levetiracetam in 58 (32.6%), carbamazepine in 36 (20.2%), valproate in 33 (18.5%), clonazepam in 9 (5.1%) and topiramate, lacosamide, lamotrigine, oxcarbazepine, clobazam, phenobarbitone, primidone and zonisamide each used in less than 4% of cases. Additional AED prescribing information, including use as prophylaxis, initial therapy, sole regimen therapy and as part of multiple regimens (either multiple monotherapies or polytherapy) can be found in supplementary material .

Patterns of seizure control

On univariate analysis, age less than 45 years at diagnosis, glioma grade, pre-operative seizure, gross total resection, re-resection, histopathological progression, radiotherapy and chemotherapy were significantly different amongst the four outcome patterns (table 1).

Grade II and III gliomas shared similar seizure outcome patterns (figure 1), with fluctuating control (pattern C) being most common. In grade IV gliomas 48%

experienced post-operative seizure freedom (pattern A) and there was an even distribution of patients in the remaining three patterns.

Median survival was significantly longer in the fluctuating control group ($p < 0.001$). In addition, median time to meeting fluctuating control criteria was 30.0 months (IQR 9.0 – 54.0 months), which was longer than the median survival in all other patterns.

To determine which clinicopathological and treatment factors were associated with seizure control pattern, variables significant on univariate analysis were included in a multivariate analysis, using pattern A as the control group (table 2).

Patients who experienced early seizure control were significantly more likely to have histological tumour progression ($p = 0.006$). Fluctuating seizure control was predicted by a lower glioma grade ($p = 0.03$), pre-operative seizure (0.047) and histological progression ($p =0.033$). While being never seizure free was strongly predicted by pre-operative seizure ($p = 0.002$) and lack of gross total resection ($p = 0.007$)

Subgroup analysis was performed on the basis of pre-operative seizure. In the cohort without pre-operative seizure, the following variables were significantly associated with seizure outcome pattern on univariate analysis: re-resection ($p = 0.002$), histological progression ($p = 0.002$) and chemotherapy ($p = 0.038$). In the cohort with pre-operative seizure, significant variables on univariate analysis were age less than 45 years ($p = 0.042$), gross total resection ($p = 0.001$) and re-resection ($p = 0.031$). Multivariate analysis was performed in each subgroup (table 3). In patients without pre-operative seizure, early seizure control was associated with histological tumour progression ($p = 0.002$). While in the cohort with pre-operative seizures, gross total resection was predictive of both early seizure control ($p = 0.014$) and never being seizure free ($p = 0.002$).

12 Month Seizure Freedom and Subsequent Relapses

Sixty-one episodes of 12-month seizure freedom were experienced by 53 patients with TAE. Fifteen (26.3%) grade IV glioma patients had one 12-month

seizure freedom period, 15 (68.2%) grade III glioma patients had one or more 12-month periods of seizure freedom and 23 (57.5%) of grade II glioma patients experienced one or more 12-month periods of seizure freedom. Two separate 12-month periods of seizure freedom were experienced by 5 grade III and 3 grade II glioma patients.

Median duration of seizure freedom was 24.7 months (range 13.0 – 112.4 months) in grade IV, 39.0 months (range 12.0 – 120.0 months) in grade III and 45.4 months (range 12.0 – 186.0 months) in grade II glioma patients. Of those experiencing a 12-month period of seizure freedom at least one subsequent seizure occurred in 13.3% (2 of 15) of grade IV, 60% (9 of 15) of grade III and 39.1% (9 of 23) of grade II glioma patients.

Terminal Seizure Freedom

To examine the effectiveness of AED regimens, we analysed patients with TAE who had at least a 12-month survival. 93 patients fulfilled this criterion and of these, thirty-two (34.4%) had achieved terminal seizure freedom of at least 12 months at last follow-up. AED taken up by these 93 patients can be found in supplementary material.

22.6% reached terminal seizure freedom of at least 12 months on their first post-operative anti-epileptic drug regimen, 6.5% on their second regimen and 5.4% on subsequent regimens (table 4). In the grade IV cohort, 16 of 34 (47.1%) with TAE achieved terminal seizure freedom of at least 6 months; 23.5% on first anti-epileptic drug regimen, 20.6% on second regimen and 2.9% on subsequent regimens.

Time to seizure terminal freedom survival analysis reflected this decrease in seizure freedom with increasing trials of AED regimens ($p < 0.001$) (figure 2A). Both the difference between 1st and 2nd regimen ($p = 0.001$) and 2nd and subsequent regimens ($p = 0.006$) were statistically significant.

The proportion of patients prescribed second and third regimens as a percentage of those who were not seizure free on their previous regimen is displayed in

figure 2B. The majority of grade II (90%) and grade IV (88%) glioma patients who did not achieve seizure freedom on first AED regimen were prescribed a second regimen. With this exception, at least 28% of all other patients were not escalated to a second or third AED regimen if they failed to achieve seizure freedom on the previous regimen.

DISCUSSION

We have conducted a longitudinal study of post-operative seizure outcomes in patients with WHO grade II-IV gliomas. The key findings are that i) distinct patterns of post-operative seizure control exist in gliomas and have specific risk factor profiles, ii) 12-month seizure freedom and subsequent relapses occur frequently in patients with grade II-III gliomas and iii) response to successive AED regimens is poorer than in the non-TAE population.

The temporal patterns of seizure control in our analysis reflected the descriptive categories in previous studies of patients with newly diagnosed epilepsy[18]. Our modified methodology utilized 6 month intervals of seizure control to classify subjects in the first 24 months. This was chosen given the relative short survival of grade IV gliomas and the clinically meaningful time period of 6 months to this patient group.

The patients in our study appear to be representative of the general glioma population. In our study, 43% and 49% of patients experienced pre-operative and post-operative seizures respectively. After allowing for glioma grade, these rates are consistent with previous large retrospective series[3; 4; 6; 20; 21]. In addition, patients with de novo grade IV gliomas who received adjuvant chemoradiotherapy had a median survival of 14.5 months, which is similar to randomized controlled trial data[22].

We hypothesize that seizure outcome patterns correspond to unique pathogenic mechanisms of TAE. Patients who experienced post-operative seizure freedom

(Pattern A) were more likely to have grade IV gliomas, no pre-operative seizures, gross total resection and a lack of histological progression. These are well recognized predictors of post-operative seizure freedom[5; 6; 23].

An early seizure control pattern was associated with histological progression on re-resection. Although not statistically significant, the majority of patients had a grade IV glioma (72%). We hypothesize that this pattern occurs in less epileptogenic tumours where the ictal onset zone is largely within tumour boundaries and re-resection successfully removes the seizure focus.

Fluctuating seizure control was the most common pattern in patients with TAE. This was driven by the high prevalence in those with grade II and III gliomas and their natural history of inevitable, but delayed progression[6; 24]. Median time to meeting fluctuating control criteria was longer than median overall survival in other patterns; this indicates that the longer survival of patients in pattern C, likely due to their younger age and lower rates of grade IV gliomas, provided them more opportunity to develop a fluctuating course. The association with histological progression on re-resection reflects either progression driven seizures or a removal of seizure focus producing seizure free periods. The fact that gross total resection was not a risk factor, suggests that fluctuating pattern is determined more by tumour recurrence rather than failure to originally resect seizure onset zone.

This dynamic process of seizure control is clearly documented in TAE [3; 5-7; 10; 25]. Rates of seizure relapse range from 24-31% in studies combining grades III and IV gliomas. Seizure control generally follows tumour activity; progression begets seizures and adjuvant chemo-radiotherapy contributes to seizure freedom, the later primarily in grade II gliomas[8; 9; 11; 26].

Despite the fact that seizure remissions clearly occur in some patients with TAE, there is little description of remission durations in the glioma literature. The small proportion of grade IV glioma patients in this analysis who achieved 12-month freedom was likely driven by their shorter overall survival. 12-month seizure freedom periods were common in grade II and III glioma patients and

were prolonged (median duration 45 and 39 months respectively). However, seizure recurrence occurred frequently, especially in those with grade III tumours, in keeping with their predilection for more aggressive recurrence.

Patients with grade II-III gliomas, should be counselled that a fluctuating course is common and that seizure recurrence can occur after long periods of seizure freedom. Any AED withdrawal must be undertaken cautiously in a patient with grade II-III glioma who has experienced a post-operative seizure, particularly if there are seizures beyond 6 months post-operatively. Our results suggest that AED withdrawal should not be considered if there is recent evidence of tumour progression.

The 'never seizure free' outcome was strongly predicted by pre-operative seizure and lack of gross total resection. We hypothesize that this outcome group represents more epileptogenic tumours where the seizure onset zone was not resected. While the tumour itself is an obvious source of seizures, the peritumoural region is increasingly recognized as the key area responsible for epileptogeneis[27; 28]. A recent intra-cranial EEG analysis reported on 9 patients with grade I-III gliomas and drug-resistant epilepsy. In all 9 patients, the seizure onset zone included tissue located beyond 1.5cm from the tumour margin [29]. Gross total resection is known to be associated with greater rates of post-operative seizure freedom[23] and this may be due to the increased chance of epileptogenic peritumoural tissue being resected. Our findings suggest that if patients have pre-operative seizures, lack of gross total resection and post-operative disabling seizures, they should have timely AED up-titration. If seizures persist, then depending on the status and location of the tumour, patients should be considered for either re-resection or a comprehensive epilepsy program assessment to identify and remove the ictal onset zone.

In large heterogenous populations of patients with newly diagnosed epilepsy, first AED regimen success is reported at 47-49.5%, second regimen 13% and subsequent regimens 4.0-5.5%[18; 30]. In our study we found markedly lower success rates with first and second regimens. The short median survival for grade IV tumours clearly limits the chance of 12-month terminal seizure

freedom. However, similarly poor AED success rates were seen with grade II-III patients, where the median follow-up was 5.2 years. This limited response may reflect the complex pathophysiology of TAE[31], which incorporates not only tumour progression, but genetic and molecular changes which may not be specifically targeted by current AEDs[32-34].

An additional cause for poor AED success is drug under-treatment. Only 63% of those 'never seizure free' met ILAE criteria as drug resistant and a large proportion of patients did not have an escalation of their AED regimen despite failing to reach seizure freedom. There are however limitations in our ability to assess adequate AED treatment, for example, some patients may not survive long enough to have 12-month terminal seizure freedom on a particular regimen, while in others, particularly higher grade gliomas, seizure control may have been adequate and therefore further AEDs would not contribute positively to quality of life. Overall, the poor AED success we described is likely multifactorial. This prescribing data has not been well reported in the TAE literature and it suggests that epileptologists should be integrated early in the management of TAE.

Given that patient enrolment commenced in 1988, the AEDs used in the cohort may not reflect current prescribing practice. In particular, enzyme inducing AEDs, such as phenytoin and carbamazepine, are now generally avoided as first line options[35]. Based on two small phase II randomized controlled trials[12; 13], several uncontrolled observational studies and largely expert opinion, levetiracetam is commonly prescribed as primary prophylaxis and for treatment following a glioma associated seizure given its favoured side effect profile and lack of interaction with typical adjuvant therapies. In addition, topiramate, lacosamide, valproate and zonisamide[36-38] have all shown various levels of benefit in small, uncontrolled studies. Though overall, it is well appreciated that the literature is lacking in high quality studies comparing the efficacy of AEDs for tumour associated epilepsy[35; 39].

The major limitation of this study is its retrospective nature and small, heterogeneous sample. Accounting for tumour progression is inherently difficult to perform in retrospective analyses. We utilized histological progression at re-resection as the most accurate and reproducible surrogate of tumour progression. However, this method will inevitably miss patients who had radiological tumour progression and deemed inappropriate for further surgery. The timing of resection in relation to seizure freedom would have been a valuable addition as it would have helped identify if seizures were attributable to histological progression or if resection led to seizure freedom In addition, as this is an analysis of real-world TAE management there is expected to be variability in prescribing patterns and across the cohort. This is mitigated by it being a single-center study.

There is a paucity of research into pharmacological therapy for post-operative TAE, with only two prospective randomized trials[12; 13]. To optimally design prospective treatment trials further data is needed. A larger population with documentation of performance status, detailed post-surgical adjuvant therapy and timing of radiological progression would be required. In addition, molecular factors, such as peritumoural glutamate concentrations[2] and isocitrate dehydrogenase mutations[33] which are known to influence tumour associated seizures, may represent additional predictors of seizure control pattern.

Key Point Box:

- Distinct patterns of post-operative seizure control exist in gliomas and have specific risk factor profiles
- Fluctuating seizure control is the most common pattern in patients with grade II-III gliomas
- Risk factors for never becoming seizure free are pre-operative seizure and lack of gross total resection
- 12-month seizure freedom and subsequent relapses occur frequently in patients with grade II-III gliomas
- Response to successive AED regimens is poorer than the non-tumour associated epilepsy population.

Ethics:

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines

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Table 1: Clinicopathological variables associated with seizure outcomes – univariate analysis

	A n (%)	B n, (%)	C n, (%)	D n, (%)	P value	Total
Patients	95	22	45	24		186
Gender (female)	44 (46.3)	12 (54.5)	15 (33.3)	11 (45.8)	0.346	82 (44.1)
Age at diagnosis (mean years +/- SD)	57.4 +/- 16.1	57.5 +/- 11.1	41.1 +/- 16.5	54.7 +/- 16.2	<0.001	53.1 +/- 17.0
Age < 45 years	24 (25.3)	3 (13.6)	25 (55.6)	7 (29.2)	0.001	59 (31.7)
Histology - A - OA/OD - AA - AOA - GBM	 10 (10.5) 8 (8.4) 9 (9.5) 2 (2.1) 66 (69.5)	 1 (4.5) 3 13.6) 2 (9.1) 0 (0.0) 16 (72.7)	 11 (24.4) 8 (17.8) 9 (20.0) 3 (6.7) 14 (31.1)	 6 (25.0) 2 (8.3) 3 (12.5) 0 (0.0) 13 (54.2)	0.007	 28 (15.1) 21 (11.3) 23 (12.4) 5 (2.7) 109 (58.6)

WHO grade - II - III - IV	18 (18.9) 11 (11.6) 66 (69.5)	4 (18.2) 2 (9.1) 16 (72.7)	19 (42.2) 12 (26.7) 14 (31.1)	8 (33.3) 3 (12.5) 13 (54.2)	0.002	49 (26.3) 28 (15.1) 109 (58.6)
Tumour location - Frontal - Occipital - Parietal - Temporal	46 (48.4) 5 (5.3) 15 (15.8) 29 (30.5)	9 (40.9) 1 (4.5) 3 (13.6) 9 (40.9)	23 (51.1) 1 (2.2) 4 (8.9) 17 (37.8)	9 (37.5) 0 (0.0) 6 (25.0) 9 (37.5)	0.741	87 (46.8) 7 (3.8) 28 (15.1) 64 (34.4)
Temporal lobe	29 (30.5)	9 (40.9)	17 (37.8)	9 (37.5)	0.712	64 (34.4)
Pre-operative seizures	28 (29.5)	10 (45.5)	27 (60.0)	16 (66.7)	<0.001	81 (43.5)
Exclusively non-disabling seizures	0 (0.0)	1 (4.5)	1 (2.2)	1 (4.2)	0.132	3 (1.6)
Drug refractory post-operative seizures	0 (0.0)	0 (0.0)	10 (22.2)	15 (62.5)	<0.001	25 (13.4)
Surgery resection - Partial - Subtotal - Gross total - Unknown	9 (9.5) 38 (40.0) 43 45.3) 5 (5.3)	2 (9.1) 14 (63.6) 6 (59.1) 0 (0.0)	5 (11.1) 9 (20.0) 26 (57.8) 5 (11.1)	4 (16.7) 13 (54.2) 4 (16.7) 3 (12.5)	0.008	20 (10.8) 74 (39.8) 79 (42.5) 13 (7.0)
Gross total resection	43 (45.3)	6 (59.1)	26 (57.8)	4 (16.7)	0.003	74

						(39.8)
Re-resection	39 (41.1)	14 (63.6)	34 (75.6)	11 (45.8)	0.001	98 (52.7)
Histopathological progression	29 (30.5)	13 (59.1)	22 (48.9)	8 (33.3)	0.034	72 (38.7)
Chemotherapy - Yes - Unknown	53 (55.8) 21 (22.1)	20 (90.9) 0 (0.0)	31 (68.9) 4 (8.9)	17 (70.8) 2 (8.3)	0.028	121 (65.1) 27 (14.5)
Radiotherapy	77 (81.1)	22 (100.0)	34 (75.6)	23 (95.8)	0.024	156 (83.9)
Follow-up (months) median, IQR	13.0 (4.0 - 28.5)	14.4 (9.7 - 36.6)	60.5 (20.4 - 98.1)	18.0 (8.6 - 65.1)	<0.001	16.9 (9.0 – 57.2)
Survival (months) median, IQR	13.1 (4.6 - 30.7)	14.7 (10.2 - 36.6)	60.5 (22.8 - 98.1)	18.1 (8.6 - 65.1)	<0.001	17.6 (9.4 - 57.7)

Abbreviations: A – astrocytoma. OA/OD – oligoastrocytoma/ oligodendroglioma, AA – anaplastic astrocytoma, AOA – anaplastic oligoastroctyoma, GBM – glioblastoma. Data represents n (%). Pattern A – no post-operative seizure; Pattern B – seizures occurring only in the first six months post-operatively and seizure free thereafter; Pattern C – fluctuating seizure control; Pattern D – never seizure free

Table 2: Predictive factors of seizure outcome patterns – multivariate analysis

Pattern	Predictive Variable	RR	95% CI lower	95% CI upper	P value
B (Early control)	Age < 45 yrs	0.240	0.056	1.034	0.055
	Grade	1.002	0.503	1.997	0.996
	Pre-operative seizure	2.879	0.992	8.353	0.052

	Gross total resection	0.333	0.107	1.037	0.058
	Histological progression	4.296	1.531	12.057	0.006
	Chemotherapy	0.550	0.252	1.201	0.134
C (Fluctuating)	Age < 45 yrs	2.025	0.841	4.875	0.115
	Grade	0.575	0.349	0.949	0.030
	Pre-operative seizure	2.290	1.011	5.190	0.047
	Gross total resection	1.666	0.747	3.718	0.213
	Histological progression	2.418	1.072	5.454	0.033
	Chemotherapy	0.893	0.559	1.425	0.634
D (Never seizure free)	Age < 45 yrs	0.564	0.161	1.978	0.371
	Grade	0.748	0.394	1.421	0.375
	Pre-operative seizure	5.330	1.868	15.212	0.002
	Gross total resection	0.189	0.056	0.630	0.007
	Histolological progression	1.389	0.491	3.928	0.535
	Chemotherapy	0.729	0.387	1.374	0.329

Re-resection had a VIF of 3.256, indicating multicollinearity and radiotherapy was a near constant predictor of pattern D; both variables caused model validity to be uncertain and were removed.

Table 3: Predictive factors of seizure outcome patterns according to pre-operative seizure – multivariate analysis

No pre-operative seizure (n=105)					
Pattern	**Predictive Variable**	**RR**	**95% CI lower**	**95% CI upper**	**P value**
Early control	Histological progression	14.453	2.748	76.009	0.002
	Chemotherapy	0.503	0.164	1.544	0.230
Fluctuating control	Histological progression	2.276	0.755	6.859	0.144
	Chemotherapy	0.533	0.263	1.082	0.082
Never seizure free	Histological progression	2.806	0.617	12.761	0.182
	Chemotherapy	0.563	0.205	1.548	0.266
Pre-operative Seizure (n=81)					
Pattern	**Predictive Variable**	**RR**	**95% CI lower**	**95% CI upper**	**P value**
Early control	Age < 45 yrs	0.169	0.015	1.857	0.146
	Gross total resection	0.106	0.018	0.641	0.014
	Re-resection	0.565	0.103	3.093	0.510
Fluctuating control	Age < 45 yrs	2.459	0.768	7.869	0.130
	Gross total resection	1.431	0.423	4.840	0.565
	Re-resection	2.557	0.702	9.311	0.155
Never seizure free	Age < 45 yrs	1.284	0.255	6.470	0.762
	Gross total resection	0.065	0.011	0.373	0.002
	Re-resection	0.295	0.057	1.524	0.145

In the subgroup without pre-operative seizure re-resection VIF was 3.974 and therefore not included in the multivariate model.

Table 4: Terminal seizure remission of 12 months with successive AED regimens

Patients with TAE and 12 month survival	All grades N=93	Grade II N=39	Grade III N=20	Grade IV N=34
12-month terminal seizure freedom^	32 (34.4)	17 (43.5)	7 (35.0)	10 (29.4)
1st AED regimen#	21 (22.6)	9 (23.1)	6 (30.1)	6 (17.6)
2nd AED regimen#	6 (6.5)	2 (5.1)	0 (0.0)	4 (11.8)
Subsequent AED regimens#	5 (5.4)	4 (10.3)	1 (5.0)	0 (0.0)

^ n, (% of those with TAE); # 12-month terminal seizure freedom on 1st, 2nd or subsequent AED regiment n, (% of those with TAE)

FIGURES:

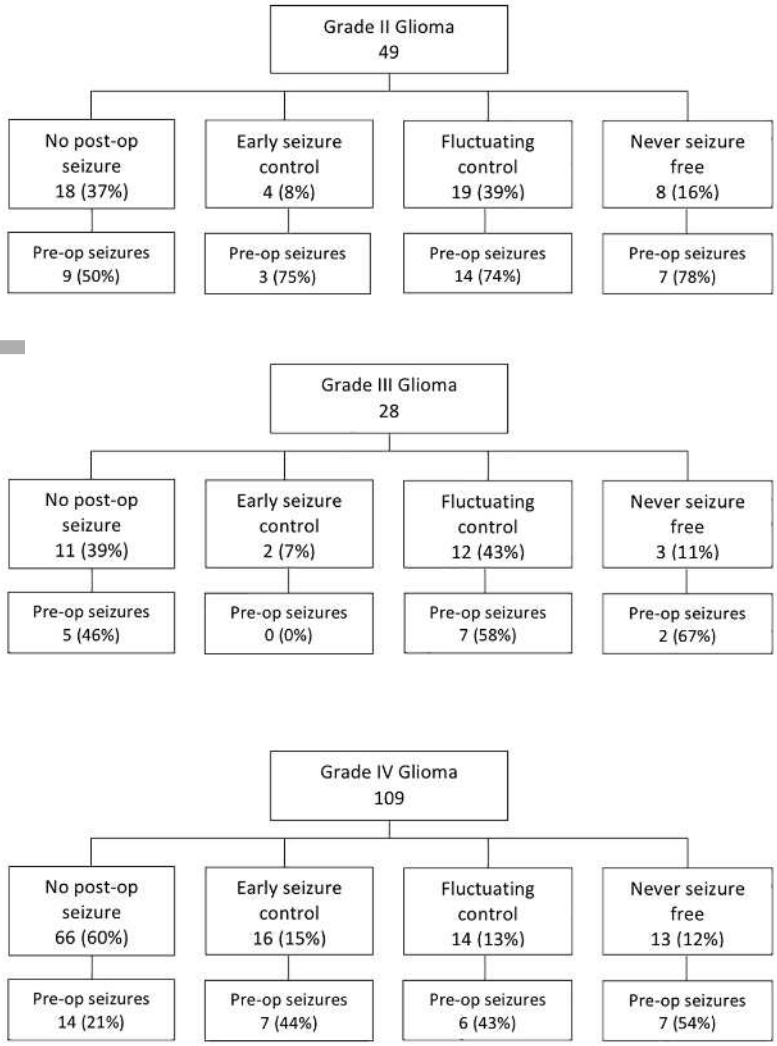
Figure 1: Seizure control patterns – flow charts

Figure 2: AED response and prescribing

2A - Cumulative probability of seizure freedom with successive AED regimens.

2B – Prescribing of AED regimens according to glioma grade

The proportion of patients prescribed second and third regimens as a percentage of those who did not achieve 12-month terminal seizure freedom on their previous AED regimen. 2nd AED regimen (blue bars) or 3rd AED regimen (green bars).



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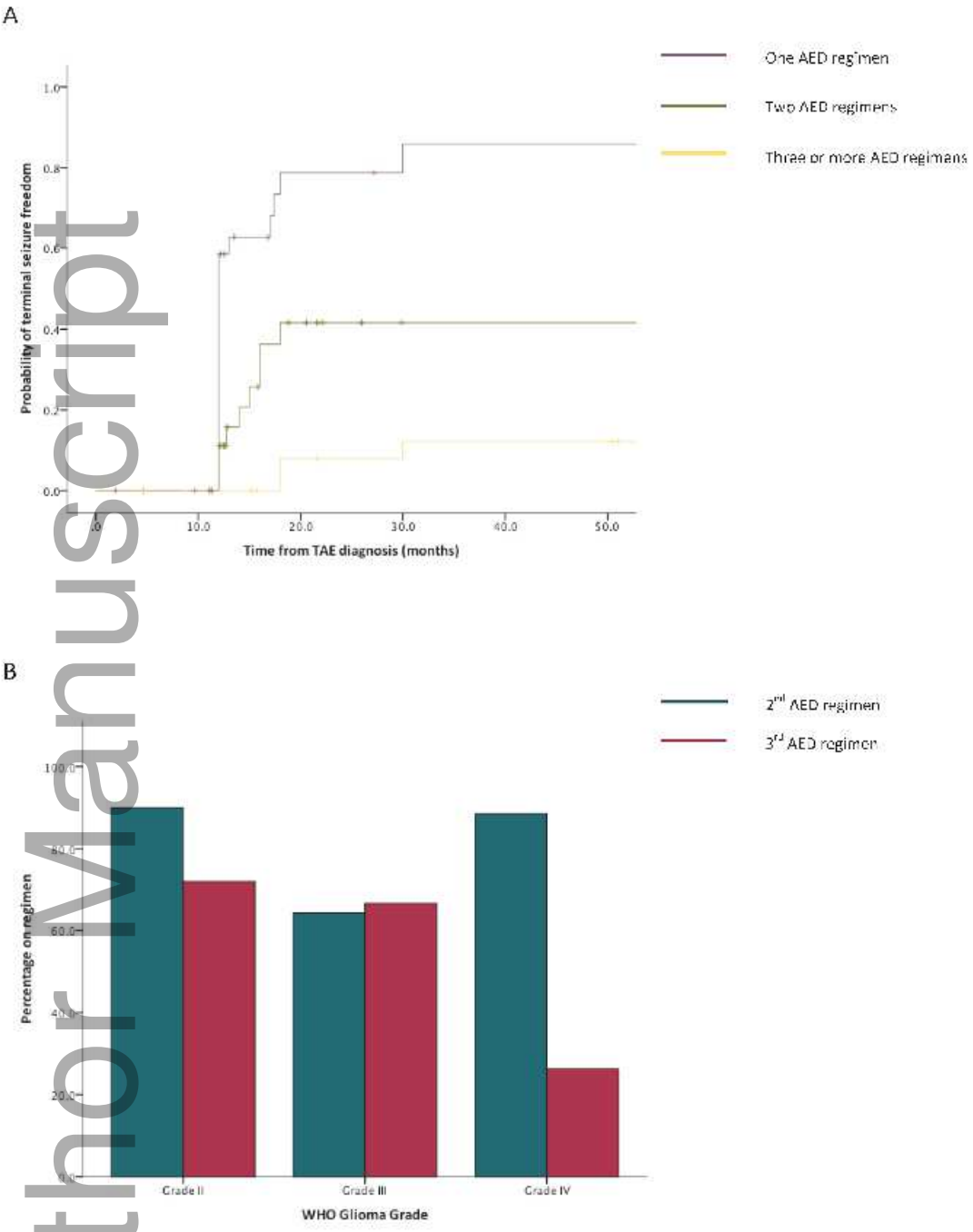

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