



Postoperative seizures in meningioma patients: improving patient selection for antiepileptic drug therapy

Abdurrahman I. Islim^{1,2,3} · Arousa Ali² · Ananyo Bagchi^{2,5} · Mohammad U. Ahmad² · Samantha J. Mills⁴ · Emmanuel Chavredakis³ · Andrew R. Brodbelt³ · Michael D. Jenkinson^{1,3}

Received: 24 May 2018 / Accepted: 25 June 2018 / Published online: 29 June 2018
© The Author(s) 2018

Abstract

Background Epilepsy is a major cause of morbidity and mortality in meningioma patients. The aims of this study were to determine which factors predispose meningioma patients to developing perioperative seizures and to understand the impact of antiepileptic drugs.

Methods Patients treated for a histologically-confirmed intracranial meningioma at the authors' institution between 2010 and 2015 were retrospectively examined. Clinical and imaging data were assessed. Multivariate analysis was performed using binary logistic regression. The effect of antiepileptic treatment was assessed using survival analysis.

Results Two hundred and eighty-three patients met the selection criteria; seizures were present in 68 preoperatively (24%) and in 48 patients (17%) following surgery. Of the 68 with preoperative seizures, 19 continued to have them, whereas de-novo seizures arose postoperatively in 29 seizure-naïve patients. Risk factors of postoperative seizures were convexity location (OR 2.05 [95% CI 1.07–3.98], $p=0.030$), fronto-parietal location (OR 4.42 [95% CI 1.49–13.16], $p=0.007$) and preoperative seizures (OR 2.65 [95% CI 1.37–5.24], $p=0.005$). The two locations, in addition to the presence of midline shift on preoperative imaging (OR 4.15 [95% CI 1.54–11.24], $p=0.005$), were significantly correlated with postoperative seizures in seizure-naïve patients. Antiepileptic treatment in patients with those risk factors reduced the possibility of seizures at any time point within the 1st year postoperatively by approximately 40%, although this did not meet statistical significance.

Conclusion Prophylactic antiepileptic treatment might be warranted in seizure-naïve meningioma patients with ≥ 1 risk factor. High-quality randomised controlled trials are required to verify those factors and to define the role of antiepileptics in meningioma practice.

Keywords Antiepileptic drugs · Epilepsy · Meningioma · Post-operative seizure

Abdurrahman I. Islim and Arousa Ali have contributed equally to this study.

✉ Abdurrahman I. Islim
a.islim@liv.ac.uk

¹ Institute of Translational Medicine, University of Liverpool, Liverpool, UK

² School of Medicine, University of Liverpool, Liverpool, UK

³ Department of Neurosurgery, The Walton Centre NHS Foundation Trust, Liverpool, UK

⁴ Department of Neuroradiology, The Walton Centre NHS Foundation Trust, Liverpool, UK

⁵ Aintree University Hospital NHS Foundation Trust, Liverpool, UK

Introduction

Whilst focal neurological deficits and incidental discovery account for the majority of new diagnoses of intracranial meningioma [1, 2], approximately a third of patients present with focal epilepsy [3]. Antiepileptic drugs (AEDs) are indicated for the treatment of brain tumour-related seizures, however, there still remains no consensus on whether prophylactic AEDs should be prescribed in seizure-naïve patients to prevent the development of postoperative seizures [4]. Epilepsy in meningioma patients is a major cause of morbidity and mortality [5, 6], but the rate at which new seizures develop in patients undergoing meningioma surgery varies, and the efficacy of AEDs in reducing post-operative seizure rates remains questionable [7, 8]. Furthermore, drug-related side effects, which can impair quality of life

(QoL) and neurocognitive function (NCF), occur in up to half of patients [5, 9, 10]. Therefore, appropriate selection of patients at risk of developing epilepsy in the peri-operative period and who might benefit from AED treatment for meningioma resection is important.

Objectives

To investigate the risk factors associated with developing peri-operative epilepsy in meningioma patients, and to determine whether AEDs reduce the risk of postoperative seizures.

Methods

Patient selection

Data for patients who underwent craniotomy and resection of a histologically-confirmed intracranial meningioma between January 2010 and December 2015 were collected retrospectively. Eligibility criteria were as follows: (i) surgery for newly-diagnosed meningioma, (ii) a follow-up period ≥ 12 months, (iii) pre- and postoperative imaging available.

Clinical and radiological characteristics

Clinical information was obtained from the medical records. Extracted preoperative data included patient demographics, seizure status and semiology (categorised according to the International League Against Epilepsy [ILAE] 2017 classification [11]), the use of AEDs (treatment or prophylaxis), clinical presentation (headache and focal neurological deficits), and the Eastern Cooperative Oncology Group performance status (ECOG). Radiological factors, recorded using the Carestream Vue picture archiving and communication system (PACS) version 11, included tumour location and volume, peritumoural signal change, midline shift, and calcification. Tumour volume was determined by manual segmentation on gadolinium-enhanced T1-weighted MRI scans. Peritumoural signal change was assessed in relation to tumour volume on T2-weighted MRI and grouped as follows: 0–5, 6–33, 34–66 and 67–100%. Zero to 5% was defined as absent oedema (based on the Visually Accessible Rembrandt Images [VASARI] MR features for gliomas [12]).

Tumours were classified according to the WHO 2007 system. Extent of resection (as recorded by the neurosurgeon in the operative notes), the presence of residual tumour on contrast-enhanced postoperative MRI, post-craniotomy

complications (hydrocephalus, CNS infection, clinically symptomatic haemorrhage and radiological haemorrhage), and the incidence of postoperative seizures were recorded. Gross total resection (GTR) was defined as Simpson grades I–III, whilst subtotal resection (STR) was defined as grades IV–V. For patients who had postoperative seizures, time to first seizure was calculated from the date of surgery to the first clinical encounter where seizure signs and symptoms were reported and judged by the attending neurosurgeon/neurologist to have constituted an epileptic seizure. Complete seizure control, which equates to a postoperative ILAE outcome of 1 [13], was determined at 12 months following this encounter.

Data analysis

Data was analysed using SPSS v24.0 (IBM, Armonk, NY, USA).

Patients were stratified based on the presence of preoperative seizures. Clinical correlates of preoperative epilepsy were accordingly determined using binary logistic regression (BLR), incorporating only factors with a significance level < 0.05 on univariate analysis, which was performed using Pearson's Chi square test for categorical variables and the Mann–Whitney U test for continuous variables. Odds ratios (ORs) with 95% confidence intervals (CI) were calculated to assess factors' effect size. Risk factors of postoperative seizures were similarly determined in all patients, and in seizure-naïve patients.

A forward stepwise selection procedure was utilised to determine the model of best fit. Model assumptions were tested by examination of residuals and the overall fit was assessed using the Hosmer and Lemeshow (H–L) test and the area under the receiver operating characteristic (ROC) curve (AUC).

The effect of AED therapy on postoperative seizure rates was assessed using a cox proportional hazards regression model. As the Driver and Vehicle Licensing agency (DVLA) in the United Kingdom (UK) sets the driving ban to a maximum duration of 12 months postoperatively in meningioma patients, time to first seizure was censored at 365 days in case of no-occurrence within the first 12 months [14]. The model encompassed two factors: AED treatment (yes/no), and a dummy variable incorporating statistically significant variables in the corresponding BLR model. Model performance was assessed using the likelihood-ratio statistic ($-2LL$) and for each variable a hazard ratio (HR) was extracted with its 95% CI.

Data validation

For tumour volume, Bland–Altman plots were performed to assess inter- and intra-observer variability. The repeated measurements were carried out on a random sample of 11 patients.

Bivariate correlation was undertaken to assess the relationships between different factors. Baseline variables that proved to be significantly correlated ($p < 0.05$) were entered as one into the BLR model.

Distribution of continuous variables was examined with normally distributed variables expressed as mean (standard deviation [SD]) and skewed variables as median (interquartile range [IQR]). Statistically significant skewed variables ($p < 0.05$) were transformed into their natural logs before being inputted into the BLR model.

Meningioma surgery and AED practice

No protocol for AED treatment is available at the authors' institution and practices are based on surgeon preference. Management decisions for meningioma are by consensus within the neuro-oncology multidisciplinary team. Patients are considered for surgery if symptomatic or asymptomatic and showing evidence of meningioma growth on surveillance imaging. Age, performance status and comorbidities are also considered. Of note, none of the patients included in this study were subject to preoperative embolisation.

Results

Study population

Demographic and clinical data are summarised in Table 1. Two hundred and eighty-three patients met the inclusion criteria. Sixty-eight patients presented with seizures, 62 of whom received preoperative AED treatment. The remaining 215 patients were seizure-naïve at presentation and 19 received prophylactic AED treatment (Fig. 1). Postoperative seizures were observed in 17% (48/283). Median time to seizure occurrence was 58 days (IQR = 442). There was one postoperative death due to epilepsy in a 69-year old male (ECOG 0, presented with epilepsy and treated with lamotrigine). Following surgical resection of a frontal convexity meningioma, the patient had a focal to bilateral seizure on day 5 after surgery and subsequently died. No other seizure-related mortalities occurred.

Predictors of preoperative seizures

Univariate analysis (Table 1) revealed parafalcine and parietal tumour locations to be associated with preoperative

seizures ($p = 0.023$, $p < 0.001$), however, the two factors were linked on bivariate correlation ($p = 0.022$) and were therefore incorporated as one variable into the BLR model. The presence of peritumoural signal intensity (6–100%) and the absence of focal neurological deficits were also correlated with preoperative seizures ($p < 0.001$, $p < 0.001$).

All three factors remained significant in the BLR model: parietal–parafalcine location (OR 2.81 [95% CI 1.44–5.46], $p = 0.002$), peritumoural signal change (OR 5.10 [95% CI 2.49–10.52], $p < 0.001$) and the absence of focal neurological deficits (OR 5.55 [95% CI 2.63–11.11], $p < 0.001$).

Predictors of postoperative seizures

Whole study population

On univariate analysis, convexity location ($p = 0.014$), fronto-parietal location ($p = 0.003$), preoperative seizures ($p = 0.006$) and the presence of peritumoural signal intensity (6–100%) ($p = 0.022$) were significantly associated with postoperative seizures (Table 2). The two meningioma locations were not correlated ($p = 0.19$). All four factors were inserted into the BLR model, in which the following remained significant: convexity location (OR 2.05 [95% CI 1.07–3.98], $p = 0.030$), fronto-parietal location (OR 4.42 [95% CI 1.49–13.16], $p = 0.007$) and preoperative seizures (OR 2.65 [95% CI 1.37–5.24], $p = 0.005$).

Seizure-naïve patients

Convexity location ($p = 0.003$), fronto-parietal location ($p < 0.001$), male sex ($p = 0.008$), midline shift ($p = 0.028$), presence of peritumoural signal intensity (6–100%) ($p = 0.017$), Simpson grade I resection ($p = 0.020$), and clinically symptomatic haemorrhage ($p = 0.038$) were statistically associated with postoperative seizures on univariate analysis (Table 2). The median meningioma volume in postoperative-seizure patients was 63.3 cm³ as opposed to 33.2 cm³ in patients who remained seizure-free ($p = 0.003$). Bland–Altman plots for intra- and inter-observer variability of meningioma volume indicated a good level of agreement.

Three factors remained significant in the BLR model: convexity location (OR 4.63 [95% CI 1.89–11.36], $p < 0.001$), fronto-parietal location (OR 7.52 [95% CI 2.04–27.78], $p = 0.002$), and the presence of midline shift on preoperative imaging (OR 4.15 [95% CI 1.54–11.24], $p = 0.005$).

Models performance

H–L tests for the previous three models were > 0.05 indicating a good fit (0.27–0.83). AUC values and plotted residuals were acceptable for the 1st and 2nd model. Parameters of the 3rd model were poor.

Table 1 Demographic and clinical data for meningioma patients and univariate analysis of preoperative seizures

	Total no. of patients (N = 283)	Preoperative seizures		OR (95% CI)	P
		Yes (N = 68)	No (N = 215)		
Focal-aware					
Motor (%)		16 (23.5)			
Non-motor (%)		9 (13.2)			
Focal-impaired awareness (%)		7 (10.3)			
Focal to bilateral (%)		36 (52.9)			
Age at diagnosis (years)					
Mean (SD)	57.7 (13.0)	56.2 (14.1)	58.2 (12.6)		0.410
Gender (%)					
Female	214 (75.6)	47 (69.1)	167 (77.7)		
Male	69 (24.4)	21 (30.9)	48 (22.3)	1.56 (0.85–2.85)	0.152
WHO grade (%)					
I	233 (82.3)	54 (79.4)	179 (83.3)		
II	47 (16.6)	13 (19.1)	34 (15.8)	1.29 (0.65–2.57)	0.469
III	3 (1.1)	1 (1.5)	2 (0.9)	1.59 (0.14–17.81)	0.707
Tumour location (%)					
Non-skull base					
Convexity	207 (73.1)	49 (72.1)	158 (73.5)	0.93 (0.51–1.71)	0.871
Parafalcine	98 (34.6)	25 (36.8)	73 (34.0)	1.13 (0.64–1.20)	0.671
Tentorial	39 (13.8)	15 (22.1)	24 (11.2)	2.25 (1.10–4.60)	0.023
Convexity/parafalcine	24 (8.5)	2 (2.9)	22 (10.2)	0.27 (0.06–1.16)	0.060
Parasagittal	17 (6.0)	2 (2.9)	15 (7.0)	0.40 (0.09–1.81)	0.222
Parasagittal	12 (4.2)	4 (5.9)	8 (3.7)	1.61 (0.47–5.55)	0.441
Posterior fossa	5 (1.8)	0	5 (2.3)	N/A	N/A
Others	12	1	11	N/A	N/A
Skull base					
Sphenoid	76 (26.9)	19 (27.9)	57 (26.5)	1.37 (0.62–3.04)	0.433
Olfactory groove	34 (12.0)	10 (14.7)	24 (11.2)	1.23 (0.42–3.40)	0.700
Suprasellar	18 (6.4)	5 (7.4)	13 (6.0)	1.23 (0.42–3.40)	0.700
Suprasellar	10 (3.5)	1 (1.5)	9 (4.2)	0.34 (0.04–2.75)	0.290
Posterior fossa	2 (0.7)	0	2 (0.9)	N/A	N/A
Others	12	3	9	N/A	N/A
Side					
Right	123 (43.5)	36 (52.9)	87 (40.5)	1.66 (0.96–2.86)	0.070
Left	125 (44.2)	27 (39.7)	98 (45.6)	0.79 (0.45–1.37)	0.395
Bilateral	35 (12.4)	5 (7.4)	30 (14.0)	0.49 (0.18–1.32)	0.150
Relation to brain lobes					
Frontal	138 (48.8)	37 (54.4)	101 (47.0)	1.35 (0.78–2.33)	0.285
Parietal	34 (12.0)	17 (25.0)	17 (7.9)	3.88 (1.85–8.13)	<0.001
Temporal	29 (10.3)	8 (11.8)	21 (9.8)	1.23 (0.52–2.92)	0.636
Fronto-parietal	16 (5.7)	3 (4.4)	13 (6.0)	0.72 (0.19–2.59)	0.611
Fronto-temporal	12 (4.2)	0	12 (5.6)	N/A	N/A
Occipital	9 (3.2)	1 (1.5)	8 (3.7)	0.39 (0.05–3.14)	0.357
Preoperative radiological characteristics					
Tumour volume (cm³)^b (%)					
Median (IQR)	24.8 (37.8)	28.1 (27.7)	37.2 (39.8)		0.195
≤ 10 cm ³	57 (20.5)	12 (17.9)	45 (21.3)		
> 10 cm ³	221 (79.5)	55 (82.1)	166 (78.7)	1.24 (0.61–2.52)	0.546
Midline shift (%)					
Yes	155 (54.8)	40 (58.8)	115 (53.5)	1.24 (0.72–2.16)	0.441
No	128 (45.2)	28 (41.2)	100 (46.5)		

Table 1 (continued)

	Total no. of patients (N = 283)	Preoperative seizures		OR (95% CI)	P
		Yes (N = 68)	No (N = 215)		
Calcification ^a (%)					
Yes	66 (23.3)	15 (22.1)	51 (23.7)	1.11 (0.57–2.13)	0.815
No	216 (76.3)	53 (77.9)	163 (75.8)		
Presence of peritumoural signal intensity (%)					
6–100% (present)	158 (55.8)	54 (79.4)	104 (48.4)	4.12 (2.16–7.85)	<0.001
0–5% (absent)	125 (44.2)	14 (20.6)	111 (51.6)		
Preoperative headaches (%)					
Yes	125 (44.2)	26 (38.2)	99 (46.0)	1.38 (0.79–2.41)	0.258
No	158 (55.8)	42 (61.8)	116 (54.0)		
Preoperative neurological deficits (%)					
Yes	201 (71.0)	33 (48.5)	168 (78.1)	3.79 (2.13–6.74)	<0.001
No	82 (29.0)	35 (51.5)	47 (21.9)		
Preoperative ECOG performance status (%)					
0–2	264 (93.3)	63 (92.6)	201 (93.5)	0.71 (0.34–1.51)	0.370
3–4	19 (6.7)	5 (7.4)	14 (6.5)		

WHO World Health Organisation, ECOG Eastern Cooperative Oncology Group

^aMissing 1 value

^bMissing 5 values

Fig. 1 The study flow chart

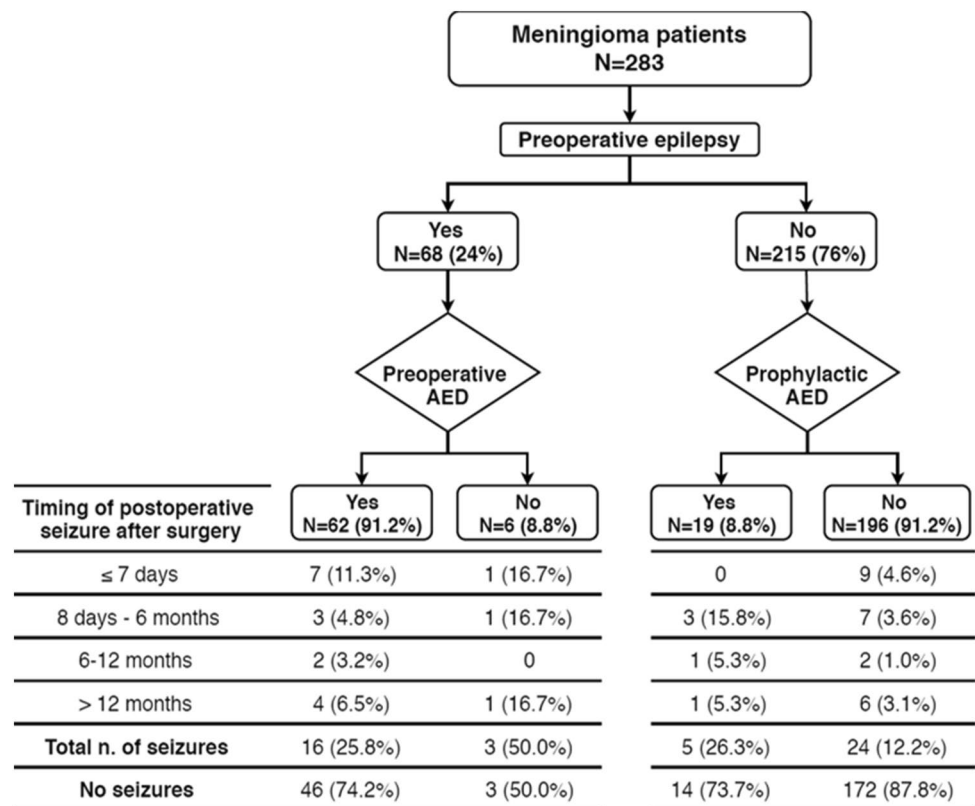


Table 2 Analysis of risk factors for postoperative seizures

Characteristic	All patients (N = 283)				Seizure-naïve patients (N = 215)			
	Postoperative seizures		Univariate analysis		Postoperative seizures		Univariate analysis	
	Yes (N = 48)	No (N = 235)	OR (95% CI)	P	Yes (N = 29)	No (N = 186)	OR (95% CI)	P
Age at diagnosis (years)								
Mean (SD)	57.6 (11.4)	57.7 (13.3)		0.751	59.0 (11.9)	58.1 (12.7)		0.744
Gender (%)								
Female	31 (64.6)	183 (77.9)			17 (58.6)	150 (80.6)		
Male	17 (35.4)	52 (22.1)	1.93 (0.99–3.76)	0.051	12 (41.4)	36 (19.4)	2.94 (1.29–6.70)	0.008
WHO grade (%)								
I	39 (81.3)	194 (82.6)			23 (79.3)	156 (83.9)		
II	8 (16.7)	39 (16.6)	1.09 (0.49–2.43)	0.829	6 (20.7)	28 (15.1)	1.36 (0.51–3.61)	0.541
III	1 (2.1)	2 (0.9)	2.48 (0.22–27.89)	0.462	0	2 (1.1)	N/A	N/A
Tumour location (%)								
Non-skull base	37 (77.1)	170 (72.3)	1.29 (0.62–2.67)	0.499	24 (82.8)	134 (72.0)	1.86 (0.67–5.14)	0.224
Convexity	24 (50.0)	74 (31.5)	2.18 (1.16–4.08)	0.014	17 (58.6)	56 (30.1)	2.83 (1.27–6.34)	0.003
Parafalcine	10 (20.8)	29 (12.3)	1.87 (0.84–4.15)	0.120	6 (20.7)	18 (9.7)	2.43 (0.87–6.76)	0.080
Tentorial	1 (2.1)	23 (9.8)	0.20 (0.03–1.49)	0.115	0	22 (11.8)	N/A	N/A
Convexity/parafalcine	1 (2.1)	16 (6.8)	0.29 (0.04–2.25)	0.209	0	15 (8.1)	N/A	N/A
Parasagittal	1 (2.1)	11 (4.7)	0.43 (0.05–3.44)	0.416	1 (3.4)	7 (3.8)	0.91 (0.11–7.71)	0.934
Posterior fossa	0	5 (2.1)	N/A	N/A	0 (0.0)	5 (2.7)	N/A	N/A
Others	0	12	N/A	N/A	0	11	N/A	N/A
Skull base	11 (22.9)	65 (27.7)			5 (17.2)	52 (28.0)		
Sphenoid	7 (14.6)	27 (11.5)	1.32 (0.54–3.22)	0.548	4 (13.8)	20 (10.8)	1.33 (0.42–4.21)	0.629
Olfactory groove	1 (2.1)	17 (6.0)	0.27 (0.03–2.10)	0.183	0	13 (7.0)	N/A	N/A
Suprasellar	0	10 (4.3)	N/A	N/A	0	9 (4.8)	N/A	N/A
Posterior fossa	0	2 (0.9)	N/A	N/A	0	2 (1.1)	N/A	N/A
Others	3	9	N/A	N/A	1	8	N/A	N/A
Side								
Right	20 (41.7)	103 (43.8)	0.92 (0.49–1.72)	0.783	10 (34.5)	77 (41.4)	0.75 (0.33–1.69)	0.480
Left	26 (54.2)	99 (42.1)	1.62 (0.87–3.03)	0.126	18 (62.1)	80 (43.0)	2.17 (0.97–4.85)	0.059
Bilateral	2 (4.2)	33 (14.0)	0.27 (0.06–1.15)	0.058	1 (3.4)	29 (15.6)	0.19 (0.03–1.48)	0.113
Relation to brain lobes								
Frontal	25 (52.1)	113 (48.1)	1.18 (0.63–2.18)	0.614	16 (55.2)	85 (36.2)	1.46 (0.67–3.21)	0.342
Parietal	5 (10.4)	29 (12.3)	0.83 (0.30–2.26)	0.709	1 (3.4)	16 (8.6)	0.38 (0.05–2.98)	0.339
Temporal	7 (14.6)	22 (9.4)	1.65 (0.66–4.12)	0.277	4 (13.8)	17 (9.1)	1.59 (0.50–5.11)	0.432
Fronto-parietal	7 (14.6)	9 (3.9)	4.35 (1.52–12.50)	0.003	6 (20.7)	7 (3.7)	6.67 (2.06–21.57)	<0.001
Fronto-temporal	1 (2.1)	11 (4.7)	0.43 (0.05–3.44)	0.416	1 (3.4)	11 (5.9)	0.57 (0.07–4.57)	0.591
Occipital	0	9 (3.3)	N/A	N/A	0	8 (4.3)	N/A	N/A
Preoperative radiological characteristics								
Tumour volume (cm³)^c (%)								
Median (IQR)	47.5 (56.3)	32.5 (35.4)		0.060	63.3 (70.3)	33.2 (36.6)		0.003
≤ 10 cm ³	6 (12.8)	51 (22.6)			3 (10.7)	42 (23.0)		
> 10 cm ³	41 (87.2)	180 (77.9)	1.94 (0.78–4.82)	0.149	25 (89.3)	141 (77.0)	2.48 (0.71–8.63)	0.141
Midline shift (%)								
Yes	30 (62.5)	125 (53.2)	1.47 (0.78–2.77)	0.238	21 (72.4)	94 (50.5)	2.56 (1.09–6.25)	0.028
No	18 (37.5)	110 (46.8)			8 (27.6)	92 (49.5)		
Calcification^a (%)								
Yes	13 (27.1)	53 (22.6)			9 (31.0)	42 (22.6)		
No	34 (70.8)	182 (77.4)	0.76 (0.38–1.55)	0.450	19 (65.5)	144 (77.4)	0.62 (0.26–1.46)	0.268

Table 2 (continued)

Characteristic	All patients (N = 283)				Seizure-naïve patients (N = 215)			
	Postoperative seizures		Univariate analysis		Postoperative seizures		Univariate analysis	
	Yes (N = 48)	No (N = 235)	OR (95% CI)	P	Yes (N = 29)	No (N = 186)	OR (95% CI)	P
Presence of peritumoural signal intensity (%)								
6–100% (present)	34 (70.8)	124 (52.8)	2.17 (1.11–4.35)	0.022	20 (69.0)	84 (45.2)	2.70 (1.16–6.25)	0.017
0–5% (absent)	14 (29.2)	111 (47.2)			9 (31.0)	102 (54.8)		
Preoperative headaches (%)								
Yes	17 (35.4)	108 (46.0)			12 (41.4)	87 (46.8)		
No	31 (64.6)	127 (54.0)	1.55 (0.81–2.95)	0.180	17 (58.6)	99 (53.2)	1.24 (0.56–2.75)	0.588
Preoperative neurological deficits (%)								
Yes	30 (62.5)	175 (74.5)			24 (82.8)	144 (77.4)		
No	18 (37.5)	60 (25.5)	1.75 (0.91–3.37)	0.093	5 (17.2)	42 (22.6)	0.71 (0.26–1.99)	0.518
Preoperative ECOG performance status (%)								
0–2	44 (91.7)	220 (93.6)			26 (89.7)	175 (94.1)		
3–4	4 (8.3)	15 (6.4)	1.41 (0.66–2.99)	0.373	3 (10.3)	11 (5.9)	2.09 (0.87–4.99)	0.093
Simpson grade of resection (%)								
GTR	42 (87.5)	191 (81.3)	1.61 (0.65–4.03)	0.303	26 (89.7)	150 (80.6)	2.08 (0.59–7.25)	0.242
1	16 (33.3)	49 (20.9)	1.95 (0.98–3.84)	0.054	11 (37.9)	36 (19.4)	2.63 (1.14–5.88)	0.020
2	24 (50.0)	129 (54.9)	0.82 (0.44–1.53)	0.535	15 (51.7)	103 (55.4)	0.86 (0.39–1.89)	0.713
3	2 (4.2)	13 (5.5)	0.75 (0.16–3.40)	0.701	0	11 (5.9)	N/A	N/A
STR	6 (12.5)	44 (18.7)			3 (10.3)	36 (19.4)		
4	6 (12.5)	44 (18.7)			3 (10.3)	36 (19.4)		
5	0	0	N/A	N/A	0	0	N/A	N/A
Postoperative residual tumour ^b (%)								
Yes	7 (14.9)	43 (18.5)			3 (10.7)	32 (17.3)		
No	40 (85.1)	189 (81.5)	1.30 (0.55–3.10)	0.554	25 (89.3)	153 (82.7)	1.74 (0.50–6.12)	0.381
Postoperative neurosurgical complications ^b (%)								
Yes	28 (58.3)	110 (46.8)	1.63 (0.86–3.09)	0.128	19 (65.5)	91 (48.9)	1.94 (0.86–4.40)	0.108
No	19 (39.6)	122 (51.9)			10 (34.5)	93 (50.0)		
Radiological haemorrhage ^b (%)								
Yes	27 (56.3)	104 (44.3)	1.66 (0.88–3.13)	0.114	18 (62.1)	85 (45.7)	1.91 (0.85–4.26)	0.112
No	20 (41.7)	128 (54.5)			11 (37.9)	99 (53.2)		
Clinical haemorrhage (%)								
Yes	4 (8.3)	11 (4.7)	1.85 (0.56–6.08)	0.303	4 (13.8)	8 (4.3)	3.57 (1.00–12.50)	0.038
No	44 (91.7)	224 (95.3)			25 (86.2)	178 (95.7)		
CNS infection (%)								
Yes	4 (8.3)	9 (3.8)	2.28 (0.67–7.74)	0.174	4 (13.8)	9 (4.8)	3.15 (0.90–10.98)	0.072
No	44 (91.7)	226 (96.2)			25 (86.2)	177 (95.2)		
Hydrocephalus (%)								
Yes	1 (2.1)	5 (2.1)	0.98 (0.11–8.57)	0.985	1 (3.4)	5 (2.7)	1.29 (0.15–11.48)	0.817
No	47 (97.9)	230 (97.9)			28 (96.6)	181 (97.3)		
Preoperative seizures (%)								
Yes	19 (39.6)	49 (20.9)	2.50 (1.28–4.76)	0.006	0	0	N/A	N/A
No	29 (60.4)	186 (79.1)			29 (100)	186 (100)		

WHO World Health Organisation, ECOG Eastern Cooperative Oncology Group, GTR gross total resection, STR subtotal resection, CNS central nervous system

^aMissing 1 value

^bMissing 4 values

^cMissing 5 values

Antiepileptic drug treatment

The study flow chart (Fig. 1) outlines AED treatment arms and consequent seizure rates. The most frequently utilised AEDs were phenytoin (48.1%) and levetiracetam (25.9%). Prophylactic AED use in seizure-naïve patients who did not develop postoperative epilepsy ranged from a single dose at surgery to 1092 days (median = 275 [IQR = 419]). AEDs in patients with complete postoperative control of preoperative epilepsy, were stopped less than 12 months after surgery in 32 (65.3%) patients, whereas 17 (34.7%) were on lifelong treatment (> 12 months) (median = 351 [IQR = 1217]) ($p=0.185$).

To examine the seizure response to AEDs, two cox regression analyses were performed: the first encompassing the whole study population and incorporating two variables: AED treatment and a dummy variable (convexity \times fronto-parietal \times preoperative seizures). The 2nd model comprised seizure-naïve patients and two variables were entered: AED treatment and one dummy variable (convexity \times fronto-parietal \times midline shift). The two models performed well ($-2LLs = 0.001$ and 0.004). Both dummy variables had HRs > 1 ($p = 0.004$, $p = 0.002$) whereas AED treatment in both models had a HR < 1 , reducing adjusted seizure risk (≥ 1 risk factor), at any time within the 1st year postoperatively, by 38 and 37% respectively, albeit this did not reach statistical significance ($p = 0.187$, $p = 0.451$; Table 3).

Twelve-month seizure control rates

One hundred and seventy-eight (90.8%) seizure-naïve patients who did not receive prophylactic AEDs remained seizure-free 12 months after surgery. The rate was slightly lower for seizure-naïve patients who were prescribed AEDs (78.9%) ($p=0.096$). Fifty (80.6%) patients who had AED-treated preoperative epilepsy were free of seizures at 12 months as opposed to 4 (66.7%) untreated patients ($p=0.427$). In total, the probability of seizure-freedom through 12 months of follow-up was 89.8% in seizure-naïve patients and 79.4% in patients with preoperative epilepsy ($p=0.029$). These rates dropped to 86.5 and 72.1% respectively beyond 12 months (Fig. 1).

Control of postoperative seizures within 12 months of their onset

Data was available in 47 patients (1 dead) and 18 (38.3%) had poorly controlled seizures. Ten out of 18 (55.6%) patients with poorly controlled epilepsy had seizures preoperatively. Of the 29 patients with controlled seizures, 8 (27.6%) patients had preoperative seizures ($p=0.015$). At this stage, AED monotherapy was being used in 11/18 (61.1%) patients with poorly controlled seizures.

Discussion

Studies addressing perioperative seizures are important for informing driving guidance and QoL in operated meningioma, and to justify the use or avoidance of prophylactic AEDs. In this cohort of 283 patients, parietal–parafalcine location, peritumoural signal change and the absence of focal neurological deficits were identified as independent predictors of preoperative seizures. Convexity and fronto-parietal locations, and the presence of preoperative seizures were significantly associated with postoperative seizures, in addition to the presence of midline shift on preoperative imaging in seizure-naïve patients. The likelihood of seizure-freedom after 12 months of follow-up was 89.7% in seizure-naïve patients and 79.4% in patients with preoperative epilepsy.

Risk factors of preoperative seizures

In our study cohort, 24% of patients presented with seizures, which is higher than those rates of previous reports which comprised fewer non-skull base meningiomas [15, 16], and more specifically those located along the falx abutting the parietal lobe, a factor which retained significance in the BLR model pertaining to preoperative seizures.

The presence of peritumoural signal change, indicative of vasogenic oedema, and the absence of focal neurological deficits preoperatively were also independently associated with preoperative seizures, consistent with the findings of prior papers [16–19]. Oedema in meningioma patients is postulated to be the product of vascular endothelial growth factor-A and is more frequently

Table 3 Cox regression model results

Model	Factor	HR (95% CI)	P
Whole study population	Preoperative AED	0.62 (0.31–1.26)	0.187
	Convexity \times FP \times preoperative seizures	1.06 (1.02–1.10)	0.004
Seizure-naïve patients	Preoperative AED	0.63 (0.20–2.05)	0.451
	Convexity \times FP \times midline shift	1.04 (1.01–1.06)	0.002

FP fronto-parietal location

observed in invasive subtypes of meningioma, although this did not prove to be the case in our study (WHO grade I: 23.2% vs. WHO grades II/III: 28%) [20, 21]. Smaller meningiomas, although statistically insignificant, were preoperatively more epileptogenic, potentially causing the development of seizures before symptoms of mass effect, such as focal neurological deficits, manifest. We postulate that smaller slow-growing meningiomas are allowed more time to disrupt the peritumoural functional environment driving epileptogenesis, whereas bigger relatively faster-growing meningiomas tend to display symptoms of mass effect before the epileptic process occurs.

Predictive factors of postoperative seizures

De-novo seizures occurred in 29 seizure-naïve patients (13.5%), 9 (4.2%) of which arose in the early postoperative period (within 1 week of surgery), which is slightly higher than the pooled frequency of 2.7% in a recent systematic review [7]. Midline shift, previously shown to play a role in epilepsy development following evacuation of intracranial haemorrhages and resection of cerebral metastases [22, 23], was likewise independently associated with postoperative seizures in seizure-naïve meningioma patients.

In keeping with previous studies [18, 24, 25], tumour location was an independent predictive factor. Convexity and fronto-parietal locations increased the risk of seizures arising by two- and fivefold respectively, and these numbers were approximately doubled for seizure-naïve patients. The reason being the proximity to cortical areas which are susceptible to epilepsy-predisposing morphological and functional alterations [26]. This also holds for fronto-parietal meningiomas located in the vicinity of the hyperexcitable primary motor and somatosensory cortices, which had an associated epilepsy incidence rate of 63% in a previous study [27, 28].

Simpson grade I resection was correlated with postoperative seizures on univariate analysis. Most patients with Simpson I resection were convexity meningiomas in our cohort (bivariate correlation, $p < 0.001$), and these are considered more susceptible to postoperative seizures, therefore the association between Simpson resection and seizures is a statistical finding that is not clinically relevant.

The association between peritumoural oedema and postoperative seizures was noted on univariate analysis, however, it did not emerge as an independent factor in the BLR model. Due to the small number of patients with seizures ($n = 48$), we did not stratify into early and late epilepsy. Vasogenic oedema tends to resolve within 2 weeks of surgery in 90% of the cases and future studies should stratify patients into early and late seizures [29].

Do AEDs have a role in reducing seizure rates postoperatively?

The general consensus, comprising reviews and one retired practice parameter by the American Academy of Neurology (AAN), is that AEDs should not be routinely used for prophylaxis [3, 4, 7, 8, 30], and specific guidelines for the administration of AEDs in meningiomas are yet to be formulated. As a result, a wide variety of AED practices are observed, firstly at a local level in our institute and secondly on a wider scale as the AANS/CNS survey demonstrated [31]. AEDs in our study were only administered to 8.1% of seizure-naïve patients compared to 63% of surgeons prescribing AEDs almost always [31]. This highlights, that for the time being, AEDs will continue to be prescribed in the neurosurgical community, despite the lack of proven benefit.

Previous studies have devised scoring systems to guide AED prescribing including the STAMPE2 prognostic index [17]. The limitation of such scoring systems is that it's difficult to estimate the reduction rate of seizures at each level and hence, the choice of a cut-off point for treatment is arbitrary. Our solution to this was to model data using survival analysis, to estimate the effect of AEDs in patients with different combinations of independent risk factors in all patients and in those seizure-naïve specifically. The hazard ratios for AED treatment in the models equate to an approximate seizure reduction rate of 40%. Although this was not statistically significant, these data could help direct the administration of AEDs, which due to side effects and impact on QoL, should not be prescribed routinely.

Choice of AED and duration of treatment

The wide variation in AED choice and duration of use in our study limits analysis of which drug might be most effective. Studies addressing optimal AED regimens are required, specifically for preoperative epilepsy patients whose seizures cease to recur for the first 2 weeks after surgery. In our study, this was observed in 49 patients of which 32 (65.3%) were on AEDs for up to 12 months. Recommendations are to allow a duration of at least 2 years of seizure-freedom before discontinuation is attempted [32]; however, this is based on AED trials that almost invariably exclude brain tumour patients from their populations, and therefore this cannot be applied to meningioma patients. The question of how long to continue AEDs could pragmatically be based around driving regulations, adverse events and QoL. Targeting a policy of 3 or 12 months of AED administration would be achieved in the context of a RCT. We could not draw any meaningful conclusions to support the use of one drug prophylactically over others. A well-designed trial is also required to address this question.

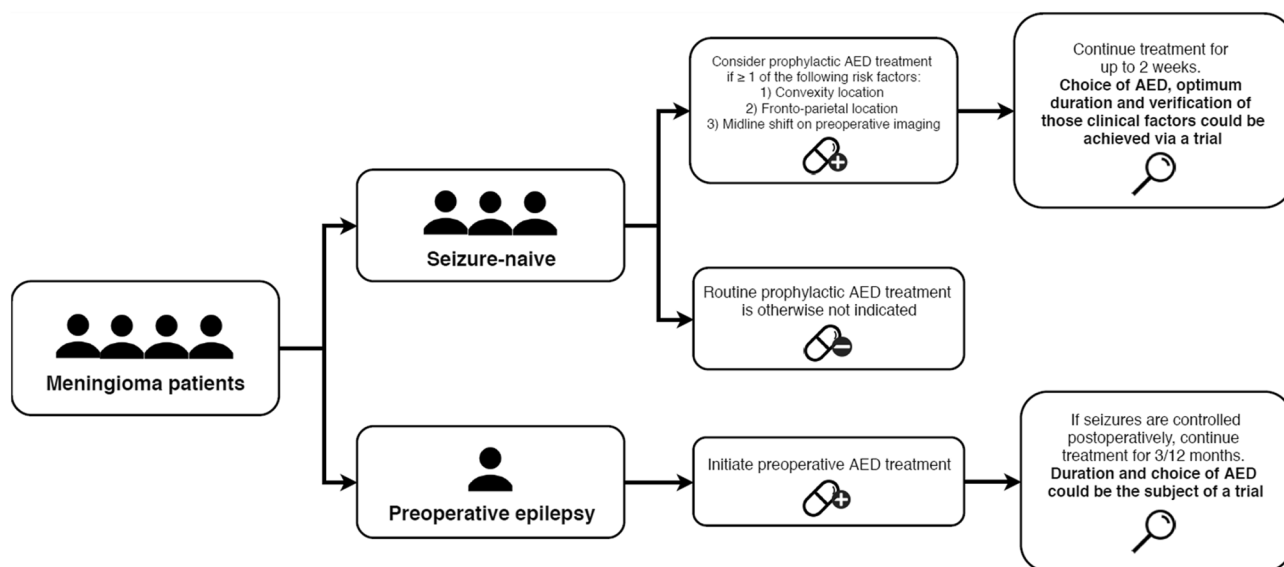


Fig. 2 Recommendations for treatment and future research

Postoperative seizure freedom

Through 12 months of follow-up, the probabilities of seizure-freedom in seizure-naïve patients and preoperative epilepsy patients were approximately 90 and 80% respectively. Beyond 12 months, the rate in patients with preoperative epilepsy dropped to 72.1%. Within 12 months of seizure-onset, likelihood of seizure freedom was 44.4% among subjects with preoperative seizures and 72.4% in patients without them. This implies that whilst an acceptable rate of seizure-control could be achieved in seizure-naïve patients, control of seizures in patients with preoperative epilepsy is more challenging. The ILAE's definition of drug resistant epilepsy emphasises that treatment failure is assessed in the context of two trialled drugs, either in combination or as monotherapies [33]. In our study, 61.1% of patients with uncontrolled seizures did not meet the aforementioned criteria. Those rates therefore need to be further evaluated following escalation of AED treatment.

Study limitations

This is a retrospective study of uneven groups operated for a meningioma in a single institution. AED choice and duration varied across patients and drug-related side effects were not recorded, therefore comparisons of drugs could not be performed. Seizure types are likely to impact patients differently however seizure semiology postoperatively was not recorded. Lastly, parameters of the three BLR models were acceptable for two and poor for the model pertaining to seizure-naïve patients.

Conclusions

Summarised in Fig. 2 are our recommendations for treatment and future research. Seizures and AEDs in meningioma patients have a great impact on QoL. The ability to identify patients at risk of seizures and to understand how AEDs augment their risk is of importance to clinicians and patients. Convexity and fronto-parietal locations as well as preoperative epilepsy are the factors most strongly related to postoperative seizures, in addition to the presence of a midline shift on preoperative imaging in seizure-naïve patients. AEDs could potentially prove beneficial in those groups of patients with an approximate seizure-reduction rate of 40%. High quality randomised controlled trials however are required to verify these factors and to determine whether AEDs have a definitive role in reducing seizure rates postoperatively.

Author contributions A.I.I: drafting and revision of the manuscript, literature review, data collection, data analysis, data interpretation. A.A: drafting and revision of the manuscript, literature review, data collection, data analysis, data interpretation. A.B: revision of the manuscript, data collection. M.U.A: revision of the manuscript, data collection. S.J.M: conceptualisation and design of the study, revision of the manuscript, data collection. E.C: conceptualisation and design of the study, revision of the manuscript. A.R.B: conceptualisation and design of the study, revision of the manuscript. M.D.J: conceptualisation and design of the study, supervision of study, drafting and revision of the manuscript, data interpretation.

Funding The authors did not receive any funding for the completion of this study.

Compliance with ethical standards

Disclosures A.I.I, A.A, A.B, M.U.A, S.J.M, E.C, A.R.B and M.D.J have no relevant disclosures to report.

Ethical approval The Institutional Review Board at the Walton Centre NHS Foundation Trust approved this study. For this type of study formal patient consent is not required.

Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

References

- Wu A, Garcia MA, Magill ST, Chen W, Vasudevan HN, Perry A et al (2017) Presenting symptoms and prognostic factors for symptomatic outcomes following resection of meningioma. *World Neurosurg*. <https://doi.org/10.1016/j.wneu.2017.12.012>
- Spasic M, Pelargos PE, Barnette N, Bhatt NS, Lee SJ, Ung N et al (2016) Incidental meningiomas: management in the neuroimaging era. *Neurosurg Clin N Am* 27(2):229–238
- Englot DJ, Magill ST, Han SJ, Chang EF, Berger MS, McDermott MW (2016) Seizures in supratentorial meningioma: a systematic review and meta-analysis. *J Neurosurg* 124(6):1552–1561
- Weston J, Greenhalgh J, Marson AG (2015) Antiepileptic drugs as prophylaxis for post-craniotomy seizures. *Cochrane Database Syst Rev* 3: Cd007286
- Tanti MJ, Marson AG, Jenkinson MD (2017) Epilepsy and adverse quality of life in surgically resected meningioma. *Acta Neurol Scand* 136(3):246–253
- van Alkemade H, de Leau M, Dieleman EM, Kardaun JW, van Os R, Vandertop WP et al (2012) Impaired survival and long-term neurological problems in benign meningioma. *Neuro Oncol* 14(5):658–666
- Islim AI, McKeever S, Kusu-Orkar TE, Jenkinson MD (2017) The role of prophylactic antiepileptic drugs for seizure prophylaxis in meningioma surgery: a systematic review. *J Clin Neurosci* 43:47–53
- Komotar RJ, Raper DM, Starke RM, Iorgulescu JB, Gutin PH (2011) Prophylactic antiepileptic drug therapy in patients undergoing supratentorial meningioma resection: a systematic analysis of efficacy. *J Neurosurg* 115(3):483–490
- Waagemans ML, van Nieuwenhuizen D, Dijkstra M, Wumkes M, Dirven CM, Leenstra S et al (2011) Long-term impact of cognitive deficits and epilepsy on quality of life in patients with low-grade meningiomas. *Neurosurgery* 69(1):72–78 discussion 8–9.
- Maschio M, Dinapoli L, Vidiri A, Pace A, Fabi A, Pompili A et al (2009) The role side effects play in the choice of antiepileptic therapy in brain tumor-related epilepsy: a comparative study on traditional antiepileptic drugs versus oxcarbazepine. *J Exp Clin Cancer Res* 28:60
- Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE et al (2017) Operational classification of seizure types by the International League Against Epilepsy: position paper of the ILAE commission for classification and terminology. *Epilepsia* 58(4):522–530
- The Cancer Imaging Archive (2015) Wiki for the VASARI feature set. The National Cancer Institute Web site. <https://wiki.cancerimagingarchive.net/display/Public/VASARI+Research+Project>. Accessed 06 Jan 2018
- Wieser HG, Blume WT, Fish D, Goldensohn E, Hufnagel A, King D et al (2001) Proposal for a new classification of outcome with respect to epileptic seizures following epilepsy surgery. *Epilepsia* 42(2):282–286
- Driver and Vehicle Licensing Agency (2016) Neurological disorders: assessing fitness to drive. <https://www.gov.uk/guidance/neurological-disorders-assessing-fitness-to-drive>. Accessed 06 Jan 2018
- Skardelly M, Rother C, Noell S, Behling F, Wuttke TV, Schittenhelm J et al (2017) Risk factors of preoperative and early postoperative seizures in patients with meningioma: a retrospective single-center cohort study. *World Neurosurg* 97:538–546
- Chaichana KL, Pendleton C, Zaidi H, Olivi A, Weingart JD, Gallia GL et al (2013) Seizure control for patients undergoing meningioma surgery. *World Neurosurg* 79(3–4):515–524
- Wirsching HG, Morel C, Gmür C, Neidert MC, Baumann CR, Valavanis A et al (2016) Predicting outcome of epilepsy after meningioma resection. *Neuro Oncol* 18(7):1002–1010
- Lieu AS, Hwang SL (2000) Intracranial meningiomas and epilepsy: incidence, prognosis and influencing factors. *Epilepsy Res* 38(1):45–52
- Chen WC, Magill ST, Englot DJ, Baal JD, Wagle S, Rick JW et al (2017) Factors associated with pre- and postoperative seizures in 1033 patients undergoing supratentorial meningioma resection. *Neurosurgery* 81(2):297–306
- Hou J, Kshetry VR, Selman WR, Bambakidis NC (2013) Peritumoral brain edema in intracranial meningiomas: the emergence of vascular endothelial growth factor-directed therapy. *Neurosurg Focus* 35(6):E2
- Kim BW, Kim MS, Kim SW, Chang CH, Kim OL (2011) Peritumoral brain edema in meningiomas: correlation of radiologic and pathologic features. *J Korean Neurosurg Soc* 49(1):26–30
- Garrett MC, Komotar RJ, Starke RM, Merkow MB, Otten ML, Connolly ES (2009) Predictors of seizure onset after intracerebral hemorrhage and the role of long-term antiepileptic therapy. *J Crit Care* 24(3):335–339
- Wu A, Weingart JD, Gallia GL, Lim M, Brem H, Bettgeowda C et al (2017) Risk factors for preoperative seizures and loss of seizure control in patients undergoing surgery for metastatic brain tumors. *World Neurosurg* 104:120–128
- Chow SY, Hsi MS, Tang LM, Fong VH (1995) Epilepsy and intracranial meningiomas. *Zhonghua yi xue za zhi = Chin Med J* 55(2):151–155
- Zhang B, Wang D, Guo Y, Yu J (2015) Clinical multifactorial analysis of early postoperative seizures in elderly patients following meningioma resection. *Mol Clin Oncol* 3(3):501–505
- van Diessen E, Diederens SJ, Braun KP, Jansen FE, Stam CJ (2013) Functional and structural brain networks in epilepsy: what have we learned? *Epilepsia* 54(11):1855–1865
- Kawaguchi T, Kameyama S, Tanaka R (1996) Peritumoral edema and seizure in patients with cerebral convexity and parasagittal meningiomas. *Neurol Med Chir (Tokyo)* 36(8):568–573 discussion 73–74.
- Stetkarova I, Stejskal L, Kofler M (2006) Tumors localized near the central sulcus may cause increased somatosensory evoked potentials. *Clin Neurophysiol* 117(6):1359–1366
- Shirovani T, Shima K, Chigasaki H (1994) Resolution of peritumoral brain edema following excision of meningioma. *Acta Neurochir* 60:416–418
- Glantz MC, Cole BF, Forsyth PA, Recht LD, Wen PY, Chamberlain MC et al (2000) Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 54(10):1886–1893
- Dewan MC, Thompson RC, Kalkanis SN, Barker FG, Hadjipanayis CG (2017) Prophylactic antiepileptic drug administration following brain tumor resection: results of a recent AANS/CNS section on tumors survey. *J Neurosurg* 126(6):1772–1778

32. Beghi E, Giussani G, Grosso S, Iudice A, La Neve A, Pisani F et al (2013) Withdrawal of antiepileptic drugs: guidelines of the Italian league against epilepsy. *Epilepsia* 54(Suppl 7):2–12
33. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G et al (2010) Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* 51(6):1069–1077