Journal of the Neurological Sciences 404 (2019) 80–85

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Review Article

Seizures in glioma patients: An overview of incidence, etiology, and therapies

Niyatee Samudra[a], Tresa Zacharias[a], Aaron Plitt[b], Bradley Lega[b], Edward Pan[a,*]

[a] Department of Neurology and Neurotherapeutics, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390, USA
[b] Department of Neurosurgery, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390, USA

ARTICLE INFO

Keywords:
seizure
epilepsy
glioma
review
cancer

ABSTRACT

Gliomas are fatal brain tumors, and even low-grade gliomas (LGGs) have an average survival of less than a decade. Seizures are a common presentation of gliomas, particularly LGGs, and substantially impact quality of life. Glioma-related seizures differ from other focal epilepsies in their pathogenesis and in the likelihood of refractory epilepsy. We review factors that predict seizure activity and response to treatment, optimal pharmacologic and surgical management of glioma-related epilepsy, and the benefit of using newer anti-seizure medications in patients with gliomas. As surgery is so often beneficial with seizure reduction, we discuss oncologic and epilepsy surgery perspectives. Treatment of gliomas has the potential to ameliorate seizures and increase rates of seizure freedom. Prospective, well-powered studies are needed to provide more definitive answers for practitioners taking care of glioma patients with seizures.

1. Introduction

Gliomas represent 81% of malignant brain tumors, with lower-grade gliomas occurring in the third and fourth decades of life [52]. In addition to treatment of the tumor itself, many patients require management of associated neurologic symptoms, including cognitive and behavioral changes, fatigue, and seizures. These symptoms can pose significant challenges to quality of life, especially as newer therapies for gliomas have extended life expectancies.

Gliomas were previously classified based on the 2007 World Health Organization Classification of Brain Tumors. They were graded on an ascending scale of I to IV, based on invasiveness, including advancing atypia, mitotic activity, necrosis and microvascular proliferation (for grade IV glioblastoma (GBM)) [10]. They have also been named according to the component glial progenitor cells (oligodendroglioma, astrocytoma). Recently, multiple molecular biomarkers have been identified that may hold promise for glioma treatment and prognostication, and molecular classification [17,28]. These markers include isocitrate dehydrogenase (IDH) 1 and 2 mutations, α-thalassemia/mental retardation syndrome X-linked (ATRX) mutation, 1p/19q co-deletion, and O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, all of which have prognostic and predictive values [46]. For "diffuse" gliomas, beyond grade I, the updated 2016 WHO classification utilizes molecular markers for further identification [17].

Glioma-related seizures were first described by Hughlings Jackson in 1882. Seizures and glioma may share common causative molecular pathways, and structural changes induced by gliomas may contribute to epilepsy [22,25,38]. Epilepsy in glioma patients carries significant morbidity, especially if not controlled [32]. Seizure management is a greater focus for the treating clinician in low grade gliomas (LGGs), particularly WHO grade II (grade I tumors are frequently benign childhood tumors), compared to high grade gliomas (HGGs), or WHO grades III and IV, given the better prognosis and higher incidence of seizures in LGGs [18]. In a recent series of several thousand patients with glioma, lower grades (oligodendroglioma/oligoastrocytoma) most commonly presented with seizures, with those affected by oligoastrocytoma having more pharmacoresistant epilepsy [4].

Here, we review the incidence and molecular etiology of seizures in glioma, as well as biomarkers and drug and surgical therapies. We also discuss the prophylactic use of anti-seizure medications and future directions for research.

1.1. Incidence and epileptic zone localization in gliomas

LGGs had an age of presentation in the 30s–40s and a seizure incidence of 70–90% in a series of 140 patients [71], followed by glioblastomas (GBMs), which had the oldest median age at presentation

* Corresponding author.
E-mail address: Edward.pan@utsouthwestern.edu (E. Pan).

https://doi.org/10.1016/j.jns.2019.07.026
Received 10 May 2019; Received in revised form 24 June 2019; Accepted 18 July 2019
Available online 19 July 2019

(60) and lowest seizure incidence (62%) in a series of 291 patients [29]. Seizures are more frequent in secondary GBMs, which progress from LGGs, as opposed to primary GBMs, which arise de novo [59]. Multifocal gliomas are also more likely to be associated with seizures [40,41]. In a study of 406 patients with HGGs, 31% developed seizures over their disease course and, of those, the majority (72%) had progressive disease [31]. Among more aggressive tumors, the tumors with a slower growth rate and smaller size were associated with higher risk for seizure in a study of 648 patients with glioma [7].

Gliomas located supratentorially and cortically have a greater risk of seizures [60]. In a series of MRIs performed on 410 LGG patients, a voxel-wise correlative analysis revealed that LGGs involving Broca's area and the inferior left primary motor area conferred a higher risk of focal seizures with preserved awareness, while those involving the right temporal-insular region were associated with higher rates of focal seizures with impaired awareness. In addition, seizures involving the left premotor area were at the highest risk to generalize [76].

Early seizures were also a predictor of seizures later in the disease course [48]. In a prospective analysis of 56 patients, seizure as a presenting symptom in HGG was associated with longer survival in patients younger than 60 years. All patients with seizures were alive at an 18-month follow up in comparison to 58.3% of those without seizures ($p = .03$) [69].

1.2. Epileptogenesis in gliomas

Seizures in gliomas are caused by cancer-induced dysfunction in the cortex as well as neurotransmitter disturbances. Rosati et al. [58,59] found a relationship between seizures and downregulation of glutamine synthetase [58]. Increased expression of Solute Carrier Family 7 Member 11 (SLC7A11), a gene coding for SXC (a cysteine/glutamate transporter) in glioma, correlates with increased glutamate levels. Glutamate excitotoxicity was associated with tumor- associated seizures and tumor growth, and possibly contributes to decreased survival [57]. Human glioma cells when implanted into immunodeficient mice release glutamate, mediated by SLC7A11 and induce seizures that were blocked by sulfasalazine [5]. In addition, mutant isocitrate dehydrogenase 1 (IDH-1), which is an important molecular marker in glioma, produces 2-hydroxyglutarate (2-HG), which has a structure similar to glutamate. Chen et al. [9,10] retrospectively showed that the presence of the IDH-1 mutation significantly increased the likelihood of preoperative seizures in patients with gliomas, and also that 2-HG increased the firing rate of rat cortical neurons, providing a plausible mechanism for epilepsy [9].

Impaired activity of potassium chloride cotransporter (KCC2), which affects inhibitory gamma-aminobutyric acid (GABA) related chloride channels, may also contribute to seizure activity in glioma [6]. Pallud et al. [53] reviewed these mechanisms of seizure generation, as well as changes in peritumoral neocortex and associated network connections that lead to epileptogenesis [53]. Other factors, such as leucine-rich, glioma-inactivated pathway (LGI-1) and mammalian target of rapamycin (mTOR), may also be involved [39,84].

1.3. Molecular biomarkers associated with seizures

Our knowledge of clinically relevant molecular biomarkers in glioma is expanding. IDH-1 mutations, associated with improved prognosis in glioma and typically found in LGGs, were associated with an increased incidence of seizures in a sample of 170 glioma patients [81]. As noted above, there may be a relationship between the product of mutant IDH-1 and the genesis of seizures. LGGs are associated with seizures that are more difficult to treat with medication [61,81]. Another prospective analysis of 56 patients with HGGs and seizures demonstrated a relationship between seizures and IDH-1 mutation and p53 overexpression [69]. 1, 2-hydroxyglutarate (2-HG), which is similar in form and function to glutamate, and is created by mutant IDH-1, contributes to seizure pathogenesis [42].

In a retrospective study of 134 patients with seizures and LGG, loss of heterozygosity (LOH) of chromosome 19q and low Ki-67 expression correlated with improved postoperative seizure control; LOH of both chromosomes 1p and 19q is typically correlated with favorable outcomes in gliomas [83]. Another study showed poor post-operative seizure control in gliomas with increased Ki-67 expression [85].

Furthermore, in a study of 147 patients with post-operative seizures and HGGs, low MGMT, a DNA repair enzyme, and epidermal growth factor receptor (EGFR) expression were significantly correlated with post-operative seizures [80]. However, low MGMT expression in gliomas has been associated with greater responsiveness to chemotherapy and radiation and, therefore, with improved survival [51]. Increased EGFR expression promotes tumorigenesis, and therefore more malignant behavior [79]. Low EGFR expression may be inferred to reflect less aggressive behavior with increased propensity for seizures, given that lower grade gliomas are known to be more frequently associated with seizures.

Of interest, although a mutation in telomerase reverse transcriptase gene promoter (TERTp) is associated with more malignant glioma type, TERTp was correlated with smaller tumors, higher likelihood of presenting with seizure, and prolonged survival in a series of 67 GBM patients [14]. A summary of molecular associations between gliomas and seizure risk is in Table 1.

2. Therapies for glioma-related seizures

2.1. Anti-seizure medications

The efficacy of one anti-seizure medication (ASM) over another for glioma-related seizures is not well documented, but evidence-based drug choice is encouraged, as in epilepsies from other causes [30]. Avoiding enzyme inducers is a preferred strategy given the concomitant use of steroids and chemotherapy for treatment of glioma [2,70]. For example, phenytoin may reduce dexamethasone levels, while valproic acid may affect coagulation parameters, namely thrombocytopenia, which can interfere with repeat surgery planning [15,63]. A systematic review of published studies on glioma-related seizure treatment using levetiracetam, a preferred agent due to minimal drug-drug interactions, suggested efficacy and a favorable safety profile [49]. NEOPLASM was

Table 1
Summary of molecular tumor characteristics reported in review associated with decreased or increased seizures in glioma patients.

	Decreased seizures	Increased seizures
Molecular markers		Impaired activity of KCC2 (affecting GABA-related chloride channels) Increased expression of SLC7A11 (cysteine/glutamate synthetase) IDH-1 mutations P53 overexpression Low expression of MGMT Low expression of EGFR
	Low Ki-67 expression LOH 1p/19q	

a 6-month retrospective observational study of patients with brain tumors treated with lacosamide, which demonstrated 66% efficacy with > 50% seizure reduction for patients, although dizziness was a notable common side effect [74]. Newer agents, such as topiramate, pregabalin, lacosamide, levetiracetam, and brivaracetam have better tolerability and fewer drug-drug interactions. In patients with gliomas, it is advised to begin anti-seizure medication after the first seizure, as there is a greater risk of recurrence [54]. A systematic review of published studies on glioma-related seizure treatment using levetiracetam, a preferred agent due to minimal drug-drug interactions, suggested efficacy and a favorable safety profile.

Some studies suggest ASMs may be of some antineoplastic utility. Brivaracetam and lacosamide have shown an antineoplastic effect on glioma cells in vitro [56], while valproic acid (a histone deacetylase inhibitor) may inhibit both glioma-genesis and glioma-associated epilepsy [23]. Valproic acid has also been suggested to prolong survival in patients with GBM [55], although a pooled analysis of several trials has suggested that neither levetiracetam nor valproic acid have benefit in glioma other than as an ASM [20].

Tapering off ASMs is another important question in glioma patients. Expert opinion suggests weighing the likelihood of seizure recurrence in LGG for those patients who have achieved long term seizure freedom [34]. A prospective observational study design to evaluate this further to help provide clinicians with more specific recommendations has been proposed [35]. In general, the decision to taper off should be individualized [21]. Patients should be counseled regarding their risk for relapse and the risks of recurrent seizures with respect to safety and driving [21]. In a cohort of patients with epilepsy, recurrent seizures occurred in 25% and 29% of patients at 1 and 2 years after anticonvulsant therapy discontinuation, respectively [3]. Relapse tends to occur shortly after anticonvulsant therapy is completely discontinued [3]. The greatest chance of discontinuation of treatment without recurrence of seizure in patients is in those patients with either seizure freedom of at least 2 years, a single seizure type, normal neurological examination and IQ, or a normal EEG on treatment [50].

Koekkoek et al. (2017) proposed criteria for tapering ASMs in glioma patients [37]. These criteria suggest that patients with midline or occipital anaplastic gliomas or GBM with near total or total resections and those with long-term seizure freedom without history of status epilepticus may benefit from ASM taper. Patient-related factors, including feeling inconvenienced or overmedicated by taking ASMs, teratogenicity, or concerns about side effects may also influence tapering off ASMs. Therefore, the decision to taper is best made by transparent discussion with the patient and by weighing risks and benefits.

2.2. Prophylactic use of anti-seizure medications

Per the 2010 American Academy of Neurology (AAN) practice guidelines, anticonvulsants should be tapered and discontinued after the first postoperative week in patients with brain tumors without seizures, in those patients who are stable, and in those experiencing side effects from their anticonvulsants [19]. Prophylactic initiation of ASM is not recommended in patients with newly diagnosed brain tumors, given sparse evidence of efficacy. Despite this, a 2015 survey of 144 tumor neurosurgeons showed that 63% of physicians prescribed ASMs post-operatively for a variable duration [11]. In 342 surgical patients with glioma, 88% received anti-seizure prophylaxis and 12% did not, with no differences between the groups in terms of perioperative seizures or need for hospital resources [12].

A 2013 prospective randomized trial of perioperative seizure prophylaxis with phenytoin in patients with brain tumor was stopped due to the high incidence of adverse effects, as well as the low likelihood that prophylaxis would help reduce seizure rates [77]. A phase II prospective, randomized trial of 146 patients with brain tumor undergoing craniotomy showed that levetiracetam was more successful than phenytoin in seizure reduction perioperatively, and it was also associated with fewer adverse events. However, the results do not imply that levetiracetam was effective prophylactically [24]. A recent review of prophylactic anticonvulsants in patients with primary glioblastoma identified a lack of evidence regarding its utility in general, as well as in the perioperative period, though there may be individual patient-specific factors to consider [75].

2.3. Surgical management of glioma-related seizures

The primary goal in glioma surgery is optimizing oncologic outcome, but improvement in seizure frequency is important, and concepts of seizure localization have been adapted from epilepsy surgery. Gross total resection (GTR) is a predictor of seizure freedom in glioma, and the extent of resection correlates with seizure freedom. A retrospective analysis of 128 patients with LGG recommended at least 80% resection to achieve seizure freedom [78]. In 773 patients (adults and children), preoperative seizure control, generalized seizures (focal aware seizures were associated with the greatest persistence), and shorter duration of seizure (< 1 year) were predictors of seizure freedom after surgery [13].

For patients presenting with seizures, invasive EEG monitoring in the pre-operative setting or electrocorticography (ECoG) in the intra-operative setting, can elucidate epileptogenic foci and help to guide resection. This approach can maximize seizure control when subtotal resection to preserve neurologic function is mandated. Epilepsy surgery is considered in non-tumoral epilepsy for focal seizures that do not respond to two or more ASM trials. The principles of epilepsy surgery rely on identifying ictal onset zone (where the seizure begins) via clinical, anatomic, and EEG features via an invasive intracranial EEG evaluation. But the epileptogenic zone, as described by Luders et al., typically goes beyond this area, extending into irritative cortex bordering the ictal onset zone [26,43]. It is necessary to more precisely identify the epileptogenic zone in order to render seizure freedom in epilepsy, and a theoretical challenge in glioma-related epilepsy is that this zone may change over time with tumor recurrence. It is sometimes difficult to define, even with invasive evaluation, how much cortex must be removed to effect acceptable seizure freedom while sparing eloquent cortex (this surgery is termed a “tailored resection”).

Good outcomes have been demonstrated in surgical treatment of seizure-inducing gliomas. Fallah et al. demonstrated 75% Engel Class I outcome (freedom from disabling seizures) at 2 years in ECoG-guided resection of pediatric tumors [16]. In temporal lobe lesions, consideration can be given to extra-lesional resection of the mesial temporal structures to assist in seizure control. Invasive EEG monitoring, ECoG-guided resection, and extra-lesional resection are strategies that impart minimal additional risk beyond the tumor resection and are a favorable, patient-centric approach to optimize seizure control. In a recent series of 108 patients with LGGs divided into two groups, one with GTR only and one with GTR with ECoG-guided further resection of epileptogenic areas, tumor location and having performed ECoG correlated with seizure freedom [82]. In this group, as in patients with epilepsy from other causes, patients with temporal lobe tumors (particularly with epileptogenicity in the anterior temporal lobe) had greater odds of seizure freedom compared to those with parietal or frontal seizures.

Technological developments in the field of epilepsy surgery have increased the number of tools available to treat seizures and glioma patients. The advent of stereo-encephalography (stereo EEG) in North America offers a less invasive option for determining seizure onset location compared to a traditional grid electrode array. Stereo EEG can identify whether glioma-adjacent structures represent seizure-onset foci, even if not clearly invaded by tumor. Laser interstitial therapy (LITT) offers possibilities of ablating deeper structures that may be seizure foci but are too difficult to access via open surgery [47]. Finally, for young patients, who may live up to 20 years with gliomas, surgeons

may consider responsive neurostimulation (RNS) for seizures emanating from eloquent cortex [27].

2.4. Early post-operative seizures

Early postoperative seizures occur within the first week of surgery [68]. These seizures are disappointing for patients and families, since the ultimate goal of surgery is to reduce seizure frequency. Patients and families may also believe that early postoperative seizures portend poor prognosis. Early postoperative seizures have been reported in about 25% of patients undergoing epilepsy surgery from any cause, and have been attributed to many factors, including tumor location, histology, tumor volume, edema, and complications related to surgery (hemorrhage, pneumocephalus) [45,67,68]. Mechanisms that lead to early postoperative seizures in patients with glioma may include aberrant levels of GABA and increased levels of glutamate in peritumoral regions in LGGs; by contrast, in HGGs, they may be more likely to be related to ischemic/anoxic mechanisms [8,86]. A retrospective review of 65 patients with frontal lobe origin seizures showed that age at seizure onset, timing of surgery, adverse operative events, and low ASM levels were not significantly different between those with and without post-operative seizures [68].

A retrospective study of 492 patients, 338 of whom had gliomas, using logistic regression, showed that risk factors for early post-operative seizures included age, smaller tumor/edema volumes ($\leq 64\ cm^3$), complete resection, diencephalic location, and high-grade tumors [66]. Again, ASMs were not shown to affect early post-operative seizures [66]. The higher frequency of early postoperative seizures seen in diencephalic tumors may be related to greater damage incurred during the operation because of greater extent of resection required to reach the tumor when it is located in deep brain structures [66]. These studies together suggest that early postoperative seizures are unlikely to increase the risk of glioma-related epilepsy and are not a reason to initiate or change ASMs.

2.5. Tumor recurrence and seizures

The recurrence or worsening of seizures following an extended period of seizure control (on or off ASMs) is highly suggestive of progression or recurrence of tumor [7,73]. This association is highly correlated with GBMs and to less of an extent in LGGs [73]. Seizure recurrence in LGGs after resection may reflect less than gross total resection (biopsy or subtotal resection). In general, however, the recurrence of seizures should prompt repeat imaging and re-evaluation of ASMs.

2.6. Effect of chemotherapy and radiation therapy on seizure control

Temozolomide, the primary chemotherapy for gliomas, may be associated with a reduction in seizure frequency. A retrospective study of 104 patients with LGG and seizures who received temozolomide showed a substantive reduction in seizure frequency (> 50% from their baseline) in approximately 40% of patients with previously uncontrolled seizures [33]. In another retrospective review of 53 patients with LGG and uncontrolled epilepsy treated with temozolomide, an association was discovered between seizure reduction after temozolomide and longer progression free survival (PFS) (median PFS 26.0 months vs 14.0 in those patients without seizure reduction; $p = .004$) [36]. A retrospective study of 39 patients with LGG treated with temozolomide compared to 30 patients not treated, in which the cohorts were matched for relevant clinical parameters, showed an improvement in seizure frequency with temozolomide in patients with oligodendroglioma, astrocytoma and oligoastrocytoma [65].

A 2013 retrospective study of grade II/III gliomas demonstrated significant seizure reduction after radiotherapy with intractable epilepsy, even in patients who did not have tumor reduction on MRI, suggesting that there could be an anti-epileptic effect of radiation therapy [62]. Radiation therapy in glioma has been proposed to be level III evidence-based recommendation for improvement of epilepsy control in patients who have undergone subtotal resection. Seizures at presentation were also considered to be a positive indicator for good response to radiotherapy [64]. Early radiotherapy in patients with LGGs, as opposed to radiotherapy after progression, was associated with better seizure control in the EORTC 22845 randomized controlled trial, although this finding may be attributed in part to tumor-specific factors [72].

3. Future research directions

There is a dearth of high-quality prospective evidence on questions of management, etiology, and prognosis in glioma-related epilepsy. Critical clinical questions include whether seizure activity or response is predictable based on tumor characteristics, whether there are sub-populations of glioma patients who would benefit from receiving ASM therapy prophylactically, the types of tumor treatments that may also mitigate epilepsy, the optimal surgical management of LGG-related epilepsy, and when ASMs can be stopped after seizure freedom is achieved. Seizure control has been proposed as a metric in LGG trials, which may help in standardizing the reporting of seizure response in the literature, leading to the generation of high-quality evidence [1]. Per expert report, this addition has been discussed in the relevant section of the American Academy of Neurology (AAN) and in the Society for Neuro-Oncology (SNO). Research in this area is critical, given the impact of seizures on quality of life for both children and adults with glioma.

Improvements in precise localization for epilepsy and oncologic surgery for gliomas may be achieved by incorporating currently existing tools in epilepsy surgery, as well as new neuroimaging technologies, including resting-state functional imaging [44]. Well-powered randomized controlled trials are needed to examine whether there is a utility in using ASMs for seizure prophylaxis in general, as well as perioperatively. Possible oncologic benefits from treatment with anticonvulsant therapy should be further investigated to examine whether these could be considered as adjunctive treatments for glioma. Novel findings in glioma research, such as discoveries of genetic prognostic factors, also make this an exciting time for research in epilepsy related to glioma.

Author contributions

Dr. Niyatee Samudra was the primary contributing author for the manuscript. Dr. Tresa Zacharias wrote and revised multiple sections. Dr. Edward Pan assisted with revisions and was the senior author. Drs Bradley Lega and Aaron Plitt contributed to the neurosurgical perspective on the manuscript.

Declaration of Competing Interest

The authors declare no conflicts of interest.

Acknowledgements

The authors are very grateful to Dr. Samarpita Sengupta for her editorial assistance and assistance with submission.

References

[1] E.K. Avila, M. Chamberlain, D. Schiff, et al., Seizure control as a new metric in assessing efficacy of tumor treatment in low-grade glioma trials, Neuro-Oncol. 19 (2016) 12–21.

[2] O. Bahr, M. Hermisson, S. Rona, et al., Intravenous and oral levetiracetam in patients with a suspected primary brain tumor and symptomatic seizures undergoing neurosurgery: the HELLO trial, Acta Neurochir. 154 (2012) 229–235 (discussion

235).
[3] A.T. Berg, S. Shinnar, Relapse following discontinuation of antiepileptic drugs: a meta-analysis, Neurology 44 (1994) 601–608.
[4] S.G. Berntsson, R.T. Merrell, E.S. Amirian, et al., Glioma-related seizures in relation to histopathological subtypes: a report from the glioma international case-control study, J. Neurol. 265 (2018) 1432–1442.
[5] S.C. Buckingham, S.L. Campbell, B.R. Haas, et al., Glutamate release by primary brain tumors induces epileptic activity, Nat. Med. 17 (2011) 1269–1274.
[6] S.L. Campbell, S. Robel, V.A. Cuddapah, et al., GABAergic disinhibition and impaired KCC2 cotransporter activity underlie tumor-associated epilepsy, Glia 63 (2015) 23–36.
[7] K.L. Chaichana, S.L. Parker, A. Olivi, et al., Long-term seizure outcomes in adult patients undergoing primary resection of malignant brain astrocytomas, Clinical article. J. Neurosurg. 111 (2009) 282–292.
[8] F. Chassoux, E. Landre, Prevention and management of postoperative seizures in neuro-oncology, Neurochirurgie 63 (2017) 197–203.
[9] H. Chen, J. Judkins, C. Thomas, et al., Mutant IDH1 and seizures in patients with glioma, Neurology 88 (2017) 1805–1813.
[10] R. Chen, M. Smith-Cohn, A.L. Cohen, et al., Glioma subclassifications and their clinical significance, Neurotherapeutics 14 (2017) 284–297.
[11] M.C. Dewan, R.C. Thompson, S.N. Kalkanis, et al., Prophylactic antiepileptic drug administration following brain tumor resection: results of a recent AANS/CNS section on Tumors survey, J. Neurosurg. 126 (2017) 1772–1778.
[12] M.C. Dewan, G.A. White-Dzuro, P.R. Brinson, et al., The influence of perioperative seizure prophylaxis on seizure rate and hospital quality metrics following glioma resection, Neurosurgery 80 (2017) 563–570.
[13] D.J. Englot, M.S. Berger, N.M. Barbaro, et al., Predictors of seizure freedom after resection of supratentorial low-grade gliomas, A review. J. Neurosurg. 115 (2011) 240–244.
[14] T.F. Ersoy, V.C. Keil, D.R. Hadizadeh, et al., New prognostic factor telomerase reverse transcriptase promotor mutation presents without MR imaging biomarkers in primary glioblastoma, Neuroradiology 59 (2017) 1223–1231.
[15] A. Fajardo, F. Olmos, L. Sarmiento, Valproic acid and the risk of perioperative bleeding. Case report and literature review, Colombian J. of Anesthesiol. 41 (2013) 61–64.
[16] A. Fallah, A.G. Weil, S. Sur, et al., Epilepsy surgery related to pediatric brain tumors: Miami Children's hospital experience, J. Neurosurg. Pediatr. 16 (2015) 675–680.
[17] S.P. Ferris, J.W. Hofmann, D.A. Solomon, et al., Characterization of gliomas: from morphology to molecules, Virchows Arch. 471 (2) (2017) 257–269.
[18] P. Gallagher, J.P. Leach, R. Grant, Time to focus on brain tumor-related epilepsy trials, Neuro-Oncol. Practice 1 (2014) 123–133.
[19] M.J. Glantz, B.F. Cole, P.A. Forsyth, et al., 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 (2000) 1886–1893.
[20] C. Happold, T. Gorlia, O. Chinot, et al., Does Valproic acid or Levetiracetam improve survival in glioblastoma? A pooled analysis of prospective clinical trials in newly diagnosed glioblastoma, J. Clin. Oncol. 34 (2016) 731–739.
[21] J.D. Hixson, Stopping antiepileptic drugs: when and why? Curr. Treat. Options Neurol. 12 (2010) 434–442.
[22] L. Huang, G. You, T. Jiang, et al., Correlation between tumor-related seizures and molecular genetic profile in 103 Chinese patients with low-grade gliomas: a preliminary study, J. Neurol. Sci. 302 (2011) 63–67.
[23] G. Huberfeld, C.J. Vecht, Seizures and gliomas–towards a single therapeutic approach, Nat. Rev. Neurol. 12 (2016) 204–216.
[24] T. Iuchi, K. Kuwabara, M. Matsumoto, et al., Levetiracetam versus phenytoin for seizure prophylaxis during and early after craniotomy for brain tumours: a phase II prospective, randomised study, J. Neurol. Neurosurg. Psychiatry 86 (2015) 1158–1162.
[25] J.H. Jackson, Localized convulsions from tumour of the brain, Brain 5 (1882) 364–374.
[26] L. Jehi, The epileptogenic zone: concept and definition, Epilepsy Curr. 18 (2018) 12–16.
[27] B.C. Jobst, R. Kapur, G.L. Barkley, et al., Brain-responsive neurostimulation in patients with medically intractable seizures arising from eloquent and other neocortical areas, 58 (2017) 1005–1014.
[28] M. Karsy, J. Guan, A.L. Cohen, et al., New molecular considerations for glioma: IDH, ATRX, BRAF, TERT, H3 K27M, Curr. Neurol. Neurosci. Rep. 17 (2017) 19.
[29] M. Kerkhof, J.C. Dielemans, M.S. van Breemen, et al., Effect of valproic acid on seizure control and on survival in patients with glioblastoma multiforme, Neuro-Oncol. 15 (2013) 961–967.
[30] S. Kerrigan, R. Grant, Antiepileptic drugs for treating seizures in adults with brain tumours, Cochrane Database Syst. Rev. (2011) Cd008586.
[31] Y.H. Kim, C.K. Park, T.M. Kim, et al., Seizures during the management of high-grade gliomas: clinical relevance to disease progression, J. Neuro-Oncol. 113 (2013) 101–109.
[32] M. Klein, N.H. Engelberts, H.M. van der Ploeg, et al., Epilepsy in low-grade gliomas: the impact on cognitive function and quality of life, Ann. Neurol. 54 (2003) 514–520.
[33] J.A. Koekkoek, L. Dirven, J.J. Heimans, et al., Seizure reduction in a low-grade glioma: more than a beneficial side effect of temozolomide, J. Neurol. Neurosurg. Psychiatry 86 (2015) 366–373.
[34] J.A. Koekkoek, L. Dirven, M.J. Taphoorn, The withdrawal of antiepileptic drugs in patients with low-grade and anaplastic glioma, Expert. Rev. Neurother. 17 (2017) 193–202.
[35] J.A. Koekkoek, M. Kerkhof, L. Dirven, et al., Withdrawal of antiepileptic drugs in glioma patients after long-term seizure freedom: design of a prospective observational study, BMC Neurol. 14 (2014) 157.
[36] J.A.F. Koekkoek, L. Dirven, J.J. Heimans, et al., Seizure reduction is a prognostic marker in low-grade glioma patients treated with temozolomide, J. Neuro-Oncol. 126 (2016) 347–354.
[37] J.A.F. Koekkoek, L. Dirven, M.J.B. Taphoorn, The withdrawal of antiepileptic drugs in patients with low-grade and anaplastic glioma, Expert. Rev. Neurother. 17 (2017) 193–202.
[38] D. Kurzwelly, U. Herrlinger, M. Simon, Seizures in patients with low-grade gliomas–incidence, pathogenesis, surgical management, and pharmacotherapy, Adv. Tech. Stand. Neurosurg. 35 (2010) 81–111.
[39] A.M. Lascano, C.M. Korff, F. Picard, Seizures and epilepsies due to Channelopathies and neurotransmitter receptor dysfunction: a parallel between genetic and immune aspects, Mol. Syndromol. 7 (2016) 197–209.
[40] J.W. Lee, P.Y. Wen, S. Hurwitz, et al., Morphological characteristics of brain tumors causing seizures, Arch. Neurol. 67 (2010) 336–342.
[41] A. Liigant, S. Haldre, A. Oun, et al., Seizure disorders in patients with brain tumors, Eur. Neurol. 45 (2001) 46–51.
[42] S.V. Liubinas, G.M. D'Abaco, B.M. Moffat, et al., IDH1 mutation is associated with seizures and protoplasmic subtype in patients with low-grade gliomas, Epilepsia 55 (2014) 1438–1443.
[43] H.O. Luders, I. Najm, D. Nair, et al., The epileptogenic zone: general principles, Epileptic Disord. 8 (Suppl. 2) (2006) S1–S9.
[44] S. Maesawa, E. Bagarinao, M. Fujii, et al., Use of network analysis to establish neurosurgical parameters in gliomas and epilepsy, Neurol. Med. Chir. (Tokyo) 56 (2016) 158–169.
[45] S. Manaka, B. Ishijima, Y. Mayanagi, Postoperative seizures: epidemiology, pathology, and prophylaxis, Neurol. Med. Chir. (Tokyo) 43 (2003) 589–600 (discussion 600).
[46] K. Masui, P.S. Mischel, G. Reifenberger, Molecular classification of gliomas, Handb. Clin. Neurol. 134 (2016) 97–120.
[47] R. Medvid, A. Ruiz, R.J. Komotar, et al., Current applications of MRI-guided laser interstitial thermal therapy in the treatment of brain neoplasms and epilepsy: a radiologic and neurosurgical overview, AJNR Am. J. Neuroradiol. 36 (2015) 1998–2006.
[48] P.L. Moots, R.J. Maciunas, D.R. Eisert, et al., The course of seizure disorders in patients with malignant gliomas, Arch. Neurol. 52 (1995) 717–724.
[49] Z.G. Nasr, B. Paravattil, K.J. Wilby, Levetiracetam for seizure prevention in brain tumor patients: a systematic review, J. Neuro-Oncol. 129 (2016) 1–13.
[50] Neurology, Practice parameter: a guideline for discontinuing antiepileptic drugs in seizure-free patients–summary statement. Report of the quality standards subcommittee of the american academy of neurology, Neurology 47 (1996) 600–602.
[51] R. Ogura, Y. Tsukamoto, M. Natsumeda, et al., Immunohistochemical profiles of IDH1, MGMT and P53: practical significance for prognostication of patients with diffuse gliomas, Neuropathology 35 (2015) 324–335.
[52] Q.T. Ostrom, L. Bauchet, F.G. Davis, et al., The epidemiology of glioma in adults: a “state of the science” review, Neuro-Oncol. 16 (2014) 896–913.
[53] J. Pallud, L. Capelle, G. Huberfeld, Tumoral epileptogenicity: how does it happen? Epilepsia 54 (Suppl. 9) (2013) 30–34.
[54] E. Perucca, Optimizing antiepileptic drug treatment in tumoral epilepsy, Epilepsia 54 (Suppl. 9) (2013) 97–104.
[55] N. Redjal, C. Reinshagen, A. Le, et al., Valproic acid, compared to other antiepileptic drugs, is associated with improved overall and progression-free survival in glioblastoma but worse outcome in grade II/III gliomas treated with temozolomide, J. Neuro-Oncol. 127 (2016) 505–514.
[56] A. Rizzo, S. Donzelli, V. Girgenti, et al., In vitro antineoplastic effects of brivaracetam and lacosamide on human glioma cells, J. Exp. Clin. Cancer Res. 36 (2017) 76.
[57] S.M. Robert, S.C. Buckingham, S.L. Campbell, et al., SLC7A11 expression is associated with seizures and predicts poor survival in patients with malignant glioma, Sci. Transl. Med. 7 (2015) (289ra286).
[58] A. Rosati, S. Marconi, B. Pollo, et al., Epilepsy in glioblastoma multiforme: correlation with glutamine synthetase levels, J. Neuro-Oncol. 93 (2009) 319–324.
[59] A. Rosati, A. Tomassini, B. Pollo, et al., Epilepsy in cerebral glioma: timing of appearance and histological correlations, J. Neuro-Oncol. 93 (2009) 395–400.
[60] R. Ruda, L. Bello, H. Duffau, et al., Seizures in low-grade gliomas: natural history, pathogenesis, and outcome after treatments, Neuro-Oncology 14 (Suppl. 4) (2012) iv55–64.
[61] R. Rudà, L. Bello, H. Duffau, et al., Seizures in low-grade gliomas: natural history, pathogenesis, and outcome after treatments, Neuro-Oncology 14 (2012) iv55–iv64.
[62] R. Rudà, U. Magliola, L. Bertero, et al., Seizure control following radiotherapy in patients with diffuse gliomas: a retrospective study, Neuro-Oncol. 15 (2013) 1739–1749.
[63] S. Ruegg, Dexamethasone/phenytoin interactions: neurooncological concerns, Swiss Med. Wkly. 132 (2002) 425–426.
[64] T.C. Ryken, I. Parney, J. Buatti, et al., The role of radiotherapy in the management of patients with diffuse low grade glioma, J. Neuro-Oncol. 125 (2015) 551–583.
[65] J.H. Sherman, K. Moldovan, H.K. Yeoh, et al., Impact of temozolomide chemotherapy on seizure frequency in patients with low-grade gliomas, J. Neurosurg. 114 (2011) 1617–1621.
[66] M. Skardelly, E. Brendle, S. Noell, et al., Predictors of preoperative and early postoperative seizures in patients with intra-axial primary and metastatic brain tumors: a retrospective observational single center study, Ann. Neurol. 78 (2015) 917–928.
[67] E.Y. Sokolova, I.A. Savin, A.B. Kadasheva, et al., The management of patients with

new epileptic seizures in the early period after resection of hemispheric tumors: two case reports and a literature review, Zh. Vopr. Neirokhir. Im. N. N. Burdenko 81 (2017) 96–103.
[68] S. Tigaran, G.D. Cascino, R.L. McClelland, et al., Acute postoperative seizures after frontal lobe cortical resection for intractable partial epilepsy, Epilepsia 44 (2003) 831–835.
[69] M. Toledo, S. Sarria-Estrada, M. Quintana, et al., Epileptic features and survival in glioblastomas presenting with seizures, Epilepsy Res. 130 (2017) 1–6.
[70] J.B. Usery, L.M. Michael 2nd, A.K. Sills, et al., A prospective evaluation and literature review of levetiracetam use in patients with brain tumors and seizures, J. Neuro-Oncol. 99 (2010) 251–260.
[71] M.S. van Breemen, R.M. Rijsman, M.J. Taphoorn, et al., Efficacy of anti-epileptic drugs in patients with gliomas and seizures, J. Neurol. 256 (2009) 1519–1526.
[72] M.J. van den Bent, D. Afra, O. de Witte, et al., Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial, Lancet 366 (2005) 985–990.
[73] C.J. Vecht, M. Kerkhof, A. Duran-Pena, Seizure prognosis in brain tumors: new insights and evidence-based management, Oncologist 19 (2014) 751–759.
[74] V. Villanueva, R. Saiz-Diaz, M. Toledo, et al., NEOPLASM study: real-life use of lacosamide in patients with brain tumor-related epilepsy, Epilepsy Behav. 65 (2016) 25–32.
[75] A.R. Wali, R.C. Rennert, S.G. Wang, et al., Prophylactic anticonvulsants in patients with primary glioblastoma, 135 (2017) 229–235.
[76] Y. Wang, T. Qian, G. You, et al., Localizing seizure-susceptible brain regions associated with low-grade gliomas using voxel-based lesion-symptom mapping, Neuro-Oncology 17 (2015) 282–288.
[77] A.S. Wu, V.T. Trinh, D. Suki, et al., A prospective randomized trial of perioperative seizure prophylaxis in patients with intraparenchymal brain tumors, J. Neurosurg. 118 (2013) 873–883.
[78] D.S. Xu, A.W. Awad, C. Mehalechko, et al., An extent of resection threshold for seizure freedom in patients with low-grade gliomas, J. Neurosurg. 128 (2018) 1084–1090.
[79] H. Xu, H. Zong, C. Ma, et al., Epidermal growth factor receptor in glioblastoma, Oncol. Lett. 14 (2017) 512–516.
[80] P. Yang, T. Liang, C. Zhang, et al., Clinicopathological factors predictive of postoperative seizures in patients with gliomas, Seizure 35 (2016) 93–99.
[81] Y. Yang, Q. Mao, X. Wang, et al., An analysis of 170 glioma patients and systematic review to investigate the association between IDH-1 mutations and preoperative glioma-related epilepsy, J. Clin. Neurosci. 31 (2016) 56–62.
[82] P.S. Yao, S.F. Zheng, F. Wang, et al., Surgery guided with intraoperative electrocorticography in patients with low-grade glioma and refractory seizures, J. Neurosurg. 128 (2018) 840–845.
[83] G. You, L. Huang, P. Yang, et al., Clinical and molecular genetic factors affecting postoperative seizure control of 183 Chinese adult patients with low-grade gliomas, Eur. J. Neurol. 19 (2012) 298–306.
[84] Y. Yuan, W. Xiang, L. Yanhui, et al., Activation of the mTOR signaling pathway in peritumoral tissues can cause glioma-associated seizures, Neurol. Sci. 38 (2017) 61–66.
[85] Y. Yuan, W. Xiang, L. Yanhui, et al., Ki-67 overexpression in WHO grade II gliomas is associated with poor postoperative seizure control, Seizure 22 (2013) 877–881.
[86] T.I. Yuen, A.P. Morokoff, A. Bjorksten, et al., Glutamate is associated with a higher risk of seizures in patients with gliomas, Neurology 79 (2012) 883–889.