

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

Seizures in low-grade gliomas: natural history, pathogenesis, and outcome after treatments.

This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/135347> since

Published version:

DOI:10.1093/neuonc/nos199

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)



UNIVERSITÀ DEGLI STUDI DI TORINO

This is an author version of the contribution published on:

Neuro Oncol. 2012 Sep;14 Suppl 4:iv55-64.

doi: 10.1093/neuonc/nos199.

The definitive version is available at:

http://neuro-oncology.oxfordjournals.org/content/14/suppl_4/iv55.long

SEIZURES IN LOW GRADE GLIOMAS: NATURAL HISTORY, PATHOGENESIS AND OUTCOME AFTER TREATMENTS

Roberta Rudà¹, Lorenzo Bello², Hugues Duffau³, Riccardo Soffietti¹.

¹. Dept. Neuro-Oncology, University of Turin and San Giovanni Battista Hospital, Italy

². Dept. Neurosurgery, University of Milan and Istituto Clinico Humanitas, Italy

³. Department of Neurosurgery, University of Montpellier and Gui de Chauliac Hospital, France

Corresponding Author

Roberta Rudà, MD, Dept Neuro-Oncology, University of Turin and San Giovanni Battista Hospital, Via Cherasco 15, 10126 Torino, Italy

Tel: +39 011 6334904

Fax: +39 011 6963487

E-mail: rudarob@hotmail.com

Seizures represent a common symptom in low-grade gliomas; when uncontrolled, they significantly contribute to patient morbidity and negatively impact quality of life. Tumor location and histology influence the risk for epilepsy. The pathogenesis of tumor-related epilepsy is multifactorial and may differ among tumor histologies (glioneuronal tumors vs diffuse grade II gliomas). Gross total resection is the strongest predictor of seizure freedom in addition to clinical factors, such as preoperative seizure duration, type, and control with antiepileptic drugs (AEDs). Epilepsy surgery may improve seizure control. Radiotherapy and chemotherapy with alkylating agents (procarbazine + CCNU + vincristine, temozolomide) are effective in reducing the frequency of seizures in patients with pharmaco-resistant epilepsy. Newer AEDs (levetiracetam, topiramate, lacosamide) seem to be better tolerated than the old AEDs (phenobarbital, phenytoin, carbamazepine), but there is lack of evidence regarding their superiority in terms of efficacy.

Keywords: antiepileptic drugs, chemotherapy, diffuse gliomas, epileptogenesis, glioneuronal tumors, radiotherapy, seizures, surgery.

Introduction

Most patients with low grade gliomas (LGGs) experience epileptic seizures as a presenting symptom.¹⁻⁴ Clinically, tumor-related seizures manifest as simple or complex partial seizures with or without secondary generalization, and in more than 50% of cases, are pharmaco-resistant. When uncontrolled, tumor-related epilepsy affects patients' quality of life, causes cognitive deterioration, and may result in significant morbidity.^{5,6} Preoperative seizures could reflect intrinsic glioma properties⁷ and are the most important factor associated with continued seizures after tumor surgery.⁸ Seizures and their sequelae can mimic tumor progression and prompt unwarranted interventions. A number of studies have established an association between epileptic seizures at disease onset and a more favorable prognosis.⁹⁻¹¹ The management of seizures represent an important part of the management of LGG^{4,12} and increasingly needs specific and multidisciplinary approaches.

Factors predisposing to seizures

Tumor location influences the risk for epilepsy.¹³ Tumors involving the frontal, temporal, and parietal lobes are more commonly associated with seizures than are occipital lesions. Infratentorial tumors

rarely cause seizures. Intractable epilepsy is particularly frequent in tumors that involve the mesiotemporal and insular (paralimbic) structures.^{14,15} This is linked to the high epileptogenicity of the temporal and insular cortex. Cortical tumors have a higher incidence of associated epilepsy than noncortical deeper lesions regardless of the involved lobe.^{15,16} Proximity to the rolandic fissure and the central sulcus also increases seizure frequency.

The frequency of seizures differs widely according to tumor type. Glioneuronal tumors, such as gangliogliomas (GGs) and disembryoplastic neuroepithelial tumors (DNTs), are typically associated with a chronic pharmaco-resistant epilepsy in up to 90%–100% of patients.¹⁷ They occur predominantly in children and young adults and in the temporal lobe. These tumors are designated by World Health Organization (WHO) classification¹⁸ as grade I tumors, thus most patients have a favorable outcome after surgical resection alone, with only rare cases of GGs that recur and/or undergo malignant transformation.^{19,20} Among DNTs, 2 histological variants, simple and complex, have been identified.²¹ Sometimes the differential diagnosis between these grade I tumors and the most common grade II gliomas is challenging due to sampling problems. The brain tissue adjacent to a GG or a DNT may frequently show an atypical cortical architecture due to a malformation of cortical development or cortical dysplasia^{17,22}; conversely, the presence of adjacent cortical maldevelopment is distinctly uncommon in grade II gliomas. Moreover, a dual pathology, such as hippocampal sclerosis in conjunction with the epileptogenic tumor, may occur. Other rare grade I gliomas, such as supratentorial pilocytic astrocytomas, pleomorphic xanthoastrocytomas, and angiocentric gliomas, which prevail in children and young adults, frequently cause seizures.¹⁷

Diffuse LGGs (WHO grade II astrocytomas, oligodendrogliomas, and oligoastrocytomas) present seizures in 60%–88% of patients.^{4,11} Among LGGs, seizures are much less frequent (47% vs 85%) in patients ≥ 60 years compared with younger patients.²³ Patients with oligodendrogliomas and oligoastrocytomas, which more often involve the cortex, are more prone to seizures than those with astrocytomas, which tend to be situated in the white matter.¹⁵ The rare protoplasmic astrocytoma, which is predominantly cortically based, can be linked to chronic epilepsy. Among grade II astrocytomas, a subtype characterized by long-term epilepsy, longer survival, and lower recurrence rate have been described.²⁴ This subtype, called isomorphic astrocytoma, is characterized by low cellularity, lack of mitotic activity, highly differentiated astrocytic cells, absence of nuclear p53 accumulation, and expression of glial microtubule-associated protein 2 and cluster of differentiation molecule 34.

No correlation has been found between seizure activity and metabolic rate of the tumor measured by PET with methionine.¹¹

Unlike high-grade gliomas, LGGs presenting with seizures have been reported to be larger on MRI than those presenting with other neurological symptoms.²⁵

Mechanisms of epileptogenesis

The pathogenesis of tumor-related seizures is multifactorial and still not fully understood.^{26,27} The mechanisms of epileptogenesis differ among tumor types.

Intrinsic epileptogenicity of glioneuronal tumors is supported by electrocorticography and surgical and immunocytochemical studies, suggesting the presence of a hyperexcitable neuronal component.²⁸ The cells of these developmental tumors can overexpress neurotransmitter receptors and neuropeptides, compromising the balance between excitation and inhibition.²⁹ The associated dysplastic disorganization of the adjacent cortex contributes to the mechanism of seizure generation. An extensive inflammatory reaction with accumulation of microglial cells in the perilesional areas has also been suggested.³⁰

Slow-growing tumors could produce an epileptogenic milieu by partial deafferentation of cortical regions, thus causing a denervation hypersensitivity.¹³

Studies using magnetoencephalographic recordings have shown that functional connectivity and network topology are significantly altered in diffuse LGG cases compared low-frequency connectivity (in particular the theta band) is pathologically increased, and the normal “small-world network” configuration is altered,^{31–33} thus leading to a lower threshold for seizures.³⁴ These differences not only

implicate the area around the tumor, but involve brainwide networks and are related to cognitive deficits.

The role of changes in peritumoral tissue is being increasingly recognized.³⁵ Neuronal density in the hippocampus of patients with mesial temporal lobe epilepsy and gliomas is normal; however, peritumoral cells may have an anomalous phenotype. Morphologic changes include aberrant migration with persistent neurons in the white matter, and pyramidal neurons with fewer inhibitory and more excitatory synapses. Intercellular connections between adjacent glial cells occur via connexin transmembrane gap junction proteins, and immunohistochemical studies have found altered expression of connexins in tumor cells and reactive astrocytes of the perilesional cortex of patients with LGGs and epilepsy.³⁶

Modern neuroimaging techniques have provided new evidence that the peritumoral microenvironment in brain tumors is substantially different from that of normal brain tissue: MR spectroscopy has demonstrated decreased levels of N-acetylaspartate, a marker of neuronal viability and function, in lesional epileptogenic cortex.³⁷ Several alterations predispose to seizure generation. The tumor can mechanically compress the surrounding normal tissue because of mass effect, inducing ischemia, hypoxia, and acidosis, which in turn induce glial cell swelling and damage. A functional consequence of acidic pH is the deregulation of sodium and calcium influx across cell membranes. Further, the influence of pH on the activity of antiepileptic drugs (AEDs) is uncertain. Changes in ionic concentrations can also contribute to neuronal excitability, and a focal disruption of the blood–brain barrier leads to the development of a seizure focus.³⁸

Brain tumors and peritumoral tissue have an altered expression of neurotransmitters and their receptors. A greater concentration of glutamate, the major excitatory amino acid neurotransmitter in the brain, has been found in brain tumor samples from patients with active epilepsy.³⁹ When invading the normal tissue, glioma cells could react to spatial constraints by releasing high levels of glutamate into the extracellular space, which induces seizures and later causes excitotoxic neuronal cell death, thereby facilitating invasion and migration.^{40–43} Ionotropic and metabotropic glutamate receptors have been shown to be overexpressed both in glioma cells and in peritumoral astrocytes.^{44–46} Activation of these receptors by glutamate could downregulate gamma-aminobutyric acid (GABA)–mediated inhibitory stimuli as a second mechanism of epileptogenesis. Alterations in levels of GABA, the main inhibitory neurotransmitter, may also contribute to tumor-associated seizures, but it remains unclear whether decreased inhibition or new excitatory activity, together with altered receptor subtype expression, is responsible for neuronal hyperexcitability.³⁵

Recent molecular–genetic findings have been described in glioneuronal tumors. A common role has been suggested for the phosphatidylinositol 3 kinase–mammalian target of rapamycin pathway in the pathogenesis of glioneuronal tumors, focal cortical dysplasias type IIB, and cortical tubers.⁴⁷ Gene expression profiling of epilepsy-associated GGs has revealed alterations in the expression of genes involved in the immune system, synaptic transmission, and cell cycle control.⁴⁸ Overall, it remains to be demonstrated that tumor-associated epilepsy and glioma growth have common genetic pathways.⁴⁹

Regarding diffuse LGGs, susceptibility candidate genes associated with tumor-related seizures have not yet been identified. In this regard, it has been reported that LGGs without LOH19q were more likely to present with seizures of secondary generalized type than those with LOH19q, thus suggesting that candidate genes could be located on chromosome 19q.⁵⁰

An actively discharging epileptic focus has the capability to induce a paroxysmal activity in areas of the brain distal to the original site and lead to a secondary epileptic focus, as occurs in cases of slow-growing tumors of the temporal lobe and long history of seizures. Both animal and human studies have demonstrated changes in synaptic plasticity and cerebral blood flow with prolonged epilepsy.⁵¹

Factors influencing preoperative seizure control

There is a lack of information on factors associated with preoperative seizure control in diffuse LGGs in the contemporary MRI era. In a recent large single-institution study, about half of patients had uncontrolled seizures.¹⁵ Associated with uncontrolled preoperative seizures were the presence of simple partial seizures, a longer duration from seizure onset, and temporal lobe involvement. Conversely, the presence of generalized seizures was associated with better seizure control.

Outcome after surgery

Surgery allows seizure control in a significant proportion of cases of diffuse LGGs, including pharmacoresistant epilepsy.^{52–58} A recent study performed a systematic review of the published literature involving 773 patients in order to identify factors associated with seizure outcome after surgery.⁵⁹ Overall, gross total resection was the strongest predictor of seizure freedom at a minimum follow-up of 6 months postsurgery: 71% of patients were seizure free (Engel class I), whereas 29% continued to have seizures (Engel classes II–IV). Interestingly, in one of the major series,¹⁵ the benefit in terms of seizure control was maintained at 12 months, and conversely only 9% of patients had no improvement or worsened. These results have improved dramatically over time as a result of the increased use of preoperative neuroimaging modalities (functional MRI, diffusion tensor imaging), intraoperative brain mapping techniques, and awake surgery, which allow more aggressive resections while preserving normal eloquent areas. Thus, in the modern era, resection can be accomplished according to functional boundaries,^{60,61} and gross total resection means resection of abnormalities of fluid attenuated inversion recovery (FLAIR) on MRI. Unfortunately, as the majority of LGGs tend to grow close to or within eloquent areas,⁶² a total or near total resection is feasible in no more than 45% of patients.⁶¹ Recently the concept of supratotal resection (ie, removal of a margin around FLAIR abnormalities) for better seizure control has been put forward.⁶³ In addition to gross total resection, preoperative seizure history may also predict outcome.⁵⁹ Patients whose seizures were well controlled by AEDs preoperatively and whose seizures were ≤ 1 year in duration achieved better seizure control postsurgery. The presence of nongeneralizing partial seizures was associated with poorer outcome. No significant difference in epilepsy outcome was found between temporal and extratemporal tumors and between adults and children. Second-line surgery can be useful for seizure control. In this setting, preoperative chemotherapy is being investigated.^{64,65}

Regarding glioneuronal tumors, similarly to diffuse gliomas, gross total resection has emerged as the strongest predictor of seizure freedom. At a minimum follow-up of 6 months after surgery 80% of patients were seizure free (Engel class I), whereas 20% continued to have seizures (Engel classes II–IV).⁶⁶ Moreover, early surgical intervention (3 years from onset of seizures) was associated with improved seizure outcome.⁶⁷ Other factors positively associated with seizure control were ≤ 1 year duration of epilepsy and the absence of secondarily generalized seizures preoperatively. Outcome did not differ significantly between patients with temporal lobe versus extratemporal tumors, histologic diagnosis of GG versus DNT, and medically controlled versus refractory seizures before surgery.⁶⁶ Favorable seizure control has also been associated with factors such as younger age at surgery, presence of large nerve cells in the tumor specimen, and absence of postoperative epileptic discharges.^{19,68,69} Overall, among patients with temporal lobe epilepsy, long-term seizure control seems better in cases of glioneuronal tumors (94%) than of diffuse gliomas (79%) and cortical dysplasias (68%).⁷⁰

A major issue related to surgery, especially in temporal and paralimbic tumors, is that the epileptogenic zone can include significant extratumoral cortical areas. Thus, 15%–20% of patients still suffer from refractory seizures after total tumor resection.^{55,57} In this setting the identification and removal of the epileptogenic zone beyond the tumor (ie, epilepsy surgery) could lead to an improved seizure outcome. Seizure outcome after lesionectomy versus lesionectomy + hippocampectomy, corticectomy, or both in patients with medically intractable seizures has been compared in several series, and improved seizure control after epilepsy surgery has been found.^{14,59,66,71–74} An open question remains regarding the use of intraoperative electrocorticography to identify the epileptogenic areas in epilepsy surgery. A series of studies tried to address this issue, leading to inconclusive results.^{14,15,59,66,75–77} It is generally recognized that the cases in which electrocorticography was used were associated with more severe and refractory epilepsy.

Role of Radiotherapy, Chemotherapy, and Targeted Therapy

Limited data are available regarding the impact of radiotherapy on tumor-related seizures. Stereotactic interstitial irradiation improves seizure control in 40%–100% of unresectable LGGs,^{78,79} and this could

be due to an increased benzodiazepine receptor density.⁷⁹ Gamma-knife radiosurgery is active in mesiotemporal tumor-related epilepsy⁸⁰ and in patients with gelastic or generalized seizures from hypothalamic hamartomas.^{81,82} Conventional radiotherapy has been reported to be effective in seizure control in 72%–100% of patients with medically intractable epilepsy and LGGs.^{83,84} Patients may become seizure free (27%–55%), and the median duration of seizure control is ~12 months but can be as long as 8 years. An indirect suggestion of the efficacy of radiotherapy on epileptic seizures comes from the EORTC (European Organisation for Research and Treatment of Cancer) 22845 phase III trial, which compared adjuvant postoperative radiotherapy versus observation in LGGs. At 1 year, 25% of patients who were irradiated had seizures, compared with 41% of patients who were not irradiated.⁸⁵ After both interstitial and conventional radiotherapy, seizure reduction may begin early during radiotherapy and is not always associated with a tumor shrinkage on MRI. In fact, among patients who had a significant reduction of seizures after radiotherapy, ≤50% had stable disease on CT/MRI.^{83,84} Thus, in addition to a direct antitumor effect, ionizing radiation may decrease seizure activity by damaging epileptogenic neurons or inducing changes of the microenvironment in the peritumoral tissue.

The efficacy of chemotherapy with alkylating agents (procarbazine + CCNU + vincristine, temozolomide) in treating LGGs, either as salvage treatment after surgery and radiotherapy or as initial treatment after surgery in symptomatic/progressive patients, is well established.¹² Seizure improvement has been obtained in 48%–100% of patients, with 20%–40% becoming seizure free.^{86–96} Clinical improvement is more frequent than objective response on MRI. The majority of patients have hyperintense lesions on T2/FLAIR images with ill-defined margins and display a minor response or stable disease. Decreased seizure frequency seems to be better correlated with decrease of uptake of methionine on PET, whereas no significant correlation between seizure response and 1p/19q codeletion has been reported so far.⁹⁶

A significant decrease of epileptic seizures, in association with volume reduction on MRI, has been reported in subependymal giant-cell astrocytomas of tuberous sclerosis after treatment with the mTOR inhibitor everolimus.^{97,98}

Efficacy and Side Effects of Antiepileptic Drugs

Studies regarding the impact of old AEDs (phenobarbital, phenytoin, carbamazepine) on tumor-related seizures are scarce. Overall, up to 70% of patients treated with these agents have recurrent seizures.⁹⁹

In the last 10 years there have been an increased number of papers focusing on the efficacy and tolerability of new AEDs in patients with brain tumors^{100–107}; however, they are all small series, either retrospective or prospective, that group together different histologies (high-grade gliomas and LGGs, metastases, meningiomas, etc). No papers have evaluated this issue in LGGs only.

From a methodological point of view, when considering the efficacy of an AED, one should take into account the frequency of seizures, the phase of the disease (at diagnosis or at the time of progression), and the concomitant antineoplastic treatment (radiotherapy, chemotherapy) that may contribute to the control of seizures. Unfortunately in the published studies these issues have not been addressed adequately. Thus, lack of studies in homogeneous subgroups of patients probably explains the wide range of seizure response that has been reported.

In this review of the different series, we have tried to extrapolate the data regarding the efficacy of AEDs in LGGs. Table 1 summarizes the series in which these data are provided.

Most reports are on levetiracetam.^{102–104,107} This drug, employed either as an add-on or as monotherapy, has displayed a high rate of seizure response (75%–100%) with a good tolerance (mild drowsiness and dizziness in a few patients). Thus, levetiracetam may be a reasonable choice for the treatment of seizures in adults with brain tumors, particularly if concerns are raised about potential interactions with other medications, such as steroids or chemotherapeutic drugs.¹⁰⁸ Two series have studied topiramate. Maschio et al.¹⁰⁵ reported promising data in 13 cases of LGGs treated as add-on or monotherapy. The rate of response was 85% (with 7 of 13 patients seizure free), but 11 of 13 patients had received concomitant antineoplastic therapies (7 chemotherapy, 4 chemoradiotherapy), and the potential contribution of these treatments was not analyzed.

Author	AED Setting	N° of LGG	Response rate (%)	Other treatments	Median follow-up
Maschio, 2008	TPM add-on and monotherapy	13/47	54% (7/13) seizure-free 31% (4/13) significant response 15% (2/13) unchanged	7/13 chemotherapy 4/13 chemotherapy + radioterapy 2/13 out of treatment	16.5 months
Rudà, unpublished	TPM add-on in persisting seizures	24/50	8% (2/24) significant response	14/24 out of treatment	9 months
Wagner, 2003	LEV add-on in persisting seizures	8/26	37.5% (3/8) seizure-free 37.5% (3/8) significant response 25% (2/8) unchanged	n. r.	12.8 months
Rosati, 2010	LEV as first-line	12/82	100% (12/12) seizure-free	n. r.	13.1 months
Newton, 2006	LEV add-on and monotherapy	7/41	43% (3/7) seizure-free 57% (4/7) significant response	many patients on anti-neoplastic treatments (not specified)	4 weeks
Striano, 2002	TGB add-on in persisting seizures	10/11	70% (7/10) significant response 30% (3/10) seizure-free	n. r.	12 months
Maschio, 2011	LCM add-on	3/14	66.5% (2/3) seizure-free 33.5% (1/3) significant response	1/3 TMZ + bevacizumab 1/3 TMZ 1/3 out of treatment	6 months

In our series (R. Ruda, unpublished data), the setting was different: topiramate was employed as an add-on in patients with low-grade tumors and an active epilepsy with poor seizure control despite ≥ 1 AED. Good seizure control was obtained in 8% of patients only. Tiagabine was investigated as an add-on in 10 patients with LGG and drug-resistant partial epilepsy.¹⁰¹ A seizure reduction $>50\%$ was observed in 7 of 10 patients, with 3 patients becoming seizure free. Adverse events were seldom observed and did not lead to a discontinuation of the drug. More recently a small series was published on the use of lacosamide.¹⁰⁹ In this prospective study, 14 patients were enrolled, including only 3 with LGGs. With a median follow-up of 6 months, the authors reported improved seizure control in all patients, with 2 of 3 being seizure free and 1 with a significant reduction of seizures. No side effects were reported. Overall, these studies suggest that side effects are less intense when newer, non-enzyme-inducing AEDs are administered in cases of brain tumors. Merrel et al.¹¹⁰ reported a retrospective comparative series of 76 cases of glioma treated with levetiracetam or phenytoin. There was no difference in seizure outcome between the phenytoin and levetiracetam groups, while patients treated with levetiracetam experienced fewer side effects and required fewer non-seizure-related dose adjustments than patients treated with phenytoin. Switching from phenytoin to levetiracetam monotherapy for seizure control following surgery of gliomas was reported to be safe and feasible in a randomized phase II study.¹¹¹

In conclusion, the available data on the efficacy and tolerability of AEDs in tumor-related epilepsy are scarce and heterogeneous due to the different histologies, the pathophysiology of seizures, the natural history of the tumor, and concomitant treatments. Needed are prospective trials focused on specific drugs in specific tumor categories. In current clinical practice, non-enzyme-inducing AEDs should be the first choice in the treatment of LGG due to a lesser incidence of side effects and lack of potential interactions with other drugs (especially steroids and chemotherapeutics).^{99,112,113} Seizure control together with a reduction of side effects should be the primary goals of therapy in cases of LGG where tumors are compatible with long survival.

Interactions between antiepileptic and anticancer agents

Interactions have been reported between AEDs and chemotherapeutic drugs, based on shared cytochrome P450 drug metabolism.¹¹⁴ Potent inducers such as phenobarbital, phenytoin, primidone, and carbamazepine may significantly reduce serum levels of nitrosoureas, procarbazine, vincristine, cyclophosphamide, ifosfamide, paclitaxel, irinotecan, topotecan, 9-aminocamptothecin, doxorubicin, teniposide, thiotepa, methotrexate, and busulfan.^{115,116} AED levels may also be affected by some chemotherapeutic agents, such as methotrexate, doxorubicin, adriamycin, and cisplatin, which decrease the serum levels of valproic acid, carbamazepine, and phenytoin. Demonstrating that temozolomide has minimal hepatic metabolism, one study documented no effect of temozolomide on levels of topiramate or oxcarbazepine in chronically treated patients.¹¹⁷

Among targeted agents, bevacizumab, a monoclonal antibody against vascular endothelial growth factor that is under investigation in recurrent grade II gliomas after standard treatments (EORTC 26091: TAVAREC), has a low potential for drug–drug interactions, whereas small tyrosine kinase inhibitor molecules (being investigated in clinical trials in malignant gliomas) such as imatinib, gefitinib, erlotinib, tipifarnib, and sorafenib are metabolized by the P450 system, thus leading to potential interactions with enzyme-inducing AEDs.¹¹⁸

Valproic acid has distinct enzyme-inhibiting properties and might reduce the metabolism of a second drug, thereby raising plasma concentrations and potentially increasing the bone marrow toxic effects of concomitant chemotherapeutic drugs such as nitrosoureas.¹¹⁹

Also, metabolism of corticosteroids is highly sensitive to enzyme induction.¹¹⁴ Enzyme-inducing AEDs increase the metabolism of various steroids, including dexamethasone, possibly resulting in inadequate control of peritumoral edema.

Mechanisms of resistance to antiepileptic drugs

The major reason for resistance of epilepsy to AEDs is overexpression of proteins belonging to the ATP-binding cassette (ABC) transporter family (in particular P-glycoprotein [P-gp]), which actively transport a variety of lipophilic drugs out of the brain capillary endothelium at the level of the BBB (the so called multidrug-resistance proteins [MRPs]). An overexpression of these proteins has been reported in tumor cells of patients with glioma¹²⁰ and in samples of brain tissue from patients with ganglioglioma¹²¹, and could lead to a diminished drug transport into the brain parenchyma. Moreover, the release of glutamate upregulates P-gp expression.¹²² A number of AEDs, including phenytoin, phenobarbital, carbamazepine, lamotrigine, and felbamate, are substrates for P-gp¹²³. Levetiracetam and valproic acid do not seem to represent a substrate for P-gp¹²³⁻¹²⁴, making these drugs attractive in brain tumor-associated epilepsy. Valproic acid might even reduce the expression of MRP1 via its histone deacetylase-inhibiting effects.¹²⁵ AEDs may fail to control seizures because of loss of receptor sensitivity¹³.

The problem of prophylaxis

Antiepileptic therapy in patients with brain tumors is recommended after the occurrence of a first seizure^{12,13}. Two meta-analyses have found no evidence to support prophylaxis with phenobarbital, phenytoin or valproic acid in patients with no history of seizures^{126,127}. A recent Cochrane review¹²⁸ has pointed out several pitfalls of both meta-analyses and trials reviewed. The strength of evidence and recommendations are weakened by clinical heterogeneity among and within trials, misclassification of levels of evidence, and selection bias in the reporting of outcome (especially adverse events). Hence, the authors prefer to state that the evidence for seizure prophylaxis is inconclusive, at best. Nonetheless, regarding implications for practice, they agree with the American Academy of Neurology subcommittee¹²⁶ that recommended against routine use of AEDs as prophylaxis in patients with brain tumors and advised discontinuance of AEDs >1 week postsurgery when used as a perioperative prophylaxis. However, many physicians still prescribe prophylactic AEDs, especially for prophylaxis of perioperative seizures¹²⁹.

It is unclear whether newer AEDs may have any benefit in preventing seizures. Only 2 retrospective trials are available. The first trial¹³⁰ evaluated oxcarbazepine for prevention of early postoperative seizures, which occurred in <3% of patients, and found similar data to those reported for old drugs; moreover, oxcarbazepine was well tolerated with rapid titration. The second study¹³⁴ compared levetiracetam with phenytoin after supratentorial neurosurgery and found that the incidence of early and late seizures was similar in both groups but that significantly fewer adverse events occurred with the use of levetiracetam, resulting in a higher retention rate after 1 year.

Conclusion

LGGs are the most epileptogenic brain tumors. Total or near total surgical resection predicts better seizure outcome for most low-grade histologies. This supports early operation not only based on oncological considerations, but also to avoid the risk of chronic epilepsy and optimize the patient's quality of life. However, no high-quality evidence, neither from randomized controlled trials nor from large registry studies, is available that addresses this question. Radiation and chemotherapy can be proposed when pharmakoresistant seizures still persist even if a true tumor progression is not evident. Newer AEDs seem to be better tolerated than the old drugs. Lastly, seizure control should always be a secondary endpoint in clinical trials in LGGs.

Conflict of interest: None declared.

References

1. Liigant A, Haldre S, Oun A, et al. Seizure disorders in patients with brain tumors. *Eur Neurol* 2001; 45:46–51.
2. Lynam LM, Lyons MK, Drazkowski JF, et al. Frequency of seizures in patients with newly diagnosed brain tumors: a retrospective review. *Clin Neurol Neurosurg* 2007; 109:634–638.
3. Rosati A, Tomassini A, Pollo B, et al. Epilepsy in cerebral glioma: timing of appearance and histological correlations. *J Neurooncol.* 2009;93:395-400.
4. Rudà R, Trevisan E, Soffietti R. Epilepsy and brain tumors. *Curr Opin Oncol* 2010;22:611-20.
5. Klein M, Engelberts NH, van der Ploeg HM, et al. Epilepsy in low-grade gliomas: the impact on cognitive function and quality of life. *Ann Neurol* 2003; 54:514–520.
6. Taphoorn MJ, Klein M. Cognitive deficits in adult patients with brain tumours. *Lancet Neurol* 2004; 3:159–168.
7. Smits A, Duffau H. Seizures and the natural history of World Health Organization grade II gliomas: a review. *Neurosurgery.* 2011; 68:1326-1333.
8. Kahlenberg CA, Fadul CE, Roberts DW, et al. Seizure prognosis of patients with low-grade tumors. *Seizure.* 2012 Jun 20.[Epub ahead of print]
9. Leighton C, Fisher B, Bauman G, et al. Supratentorial low-grade glioma in adults: an analysis of prognostic factors and timing of radiation. *J Clin Oncol* 1997;15:1294-301.
10. Pignatti F, van den Bent MJ, Curran D, et al. Prognostic factors for survival in adult patients with cerebral lowgrade glioma. *J Clin Oncol* 2002;20:2076-2084.
11. Danfors T, Ribom D, Berntsson SG, et al. Epileptic seizures and survival in early disease of grade 2 gliomas. *Eur J Neurol* 2009; 16:823–831.
12. Soffietti R, Baumert BG, Bello L, et al; Guidelines on management of low-grade gliomas: report of an EFNS-EANO Task Force. *Eur J Neurol* 2010;17:1124-1133
13. van Breemen MS, Wilms EB, Vecht CJ. Epilepsy in patients with brain tumours: epidemiology, mechanisms, and management. *Lancet Neurol* 2007; 6:421–430.
14. Duffau H, Capelle L, Lopes M, et al. Medically intractable epilepsy from insular low-grade gliomas: improvement after an extended lesionectomy. *Acta Neurochir* 2002; 144:563–572.
15. Chang EF, Potts MB, Keles GE, et al. Seizure characteristics and control following resection in 332 patients with low-grade gliomas. *J Neurosurg* 2008; 108:227–235.
16. You G, Sha ZY, Yan W, et al. Seizure characteristics and outcomes in 508 Chinese adult patients undergoing primary resection of low-grade gliomas: a clinicopathological study. *Neuro Oncol* 2012;14:230-241
17. Prayson RA. Diagnostic challenges in the evaluation of chronic epilepsy-related surgical neuropathology. *Am J Surg Pathol* 2010; 34:e1–e13.
18. Louis DN, Ohgaki H, Wiestler OD, et al. The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathol* 2007; 114:97–109.
19. Luyken C, Blümcke I, Fimmers R, et al. Supratentorial gangliogliomas: histopathologic grading and tumor recurrence in 184 patients with a median follow-up of 8 years. *Cancer* 2004; 101:146–155.
20. Majores M, von Lehe M, Fassunke J, et al. Tumor recurrence and malignant progression of gangliogliomas. *Cancer* 2008; 113:3355–3363.
21. Campos AR, Clusmann H, von Lehe M, et al. Simple and complex dysembryoplastic neuroepithelial tumors (DNT) variants: clinical profile, MRI, and histopathology. *Neuroradiology* 2009; 51:433–443
22. Blümcke I, Vinters HV, Armstrong D, et al. Malformations of cortical development and epilepsies: neuropathological findings with emphasis on focal cortical dysplasia. *Epileptic Disord* 2009; 11:181–193.
23. Kaloshi G, Psimaras D, Mokhtari K, et al. Supratentorial low-grade gliomas in older patients. *Neurology* 2009; 73:2093–2098.
24. Schramm J, Luyken C, Urbach H, et al. Evidence for a clinically distinct new subtype of grade II astrocytomas in patients with long-term epilepsy. *Neurosurgery* 2004; 55:340–347.
25. Lee JW, Wen PY, Hurwitz S, et al. Morphological characteristics of brain tumors causing seizures. *Arch Neurol* 2010; 67:336–342.

26. Beaumont A, Whittle IR. The pathogenesis of tumour associated epilepsy. *Acta Neurochir* 2000; 142:1–15.
27. Schaller B, Rüegg SJ. Brain tumor and seizures: pathophysiology and its implications for treatment revisited. *Epilepsia* 2003; 44:1223–1232
28. Ferrier CH, Aronica E, Leijten FS, et al. Electrographic discharge patterns in glioneuronal tumors and focal cortical dysplasia. *Epilepsia* 2006; 47:1477–1486.
29. Rajneesh KF, Binder DK. Tumor-associated epilepsy. *Neurosurg Focus* 2009; 27:E4.
30. Aronica E, Gorter JA, Redeker S, et al. Distribution, characterization and clinical significance of microglia in glioneuronal tumours from patients with chronic intractable epilepsy. *Neuropathol Appl Neurobiol* 2005; 31:280–291.
31. Bartolomei F, Bosma I, Klein M, et al. How do brain tumors alter functional connectivity? A magnetoencephalography study. *Ann Neurol* 2006; 59:128–138.
32. Bosma I, Douw L, Bartolomei F, et al. Synchronized brain activity and neurocognitive function in patients with low-grade glioma: a magnetoencephalography study. *Neuro Oncol* 2008;10:734-744.
33. Douw L, van Dellen E, de Groot M, et al. Epilepsy is related to theta band brain connectivity and network topology in brain tumor patients. *BMC Neurosci* 2010;11:103.
34. Ponten SC, Bartolomei F, Stam CJ. Small-world networks and epilepsy: graph theoretical analysis of intracerebrally recorded mesial temporal lobe seizures. *Clin Neurophysiol* 2007; 118:918–92
35. Shamji MF, Fric-Shamji EC, Benoit BG. Brain tumors and epilepsy: pathophysiology of peritumoral changes. *Neurosurg Rev* 2009; 32:275–284.
36. Aronica E, Gorter JA, Jansen GH, et al. Expression of connexin 43 and connexin 32 gap-junction proteins in epilepsy-associated brain tumors and in the perilesional epileptic cortex. *Acta Neuropathol* 2001; 101:449–459.
37. Chernov MF, Kubo O, Hayashi M, et al. Proton MRS of the peritumoral brain. *J Neurol Sci* 2005; 228:137–142.
38. Ivens S, Kaufer D, Flores LP, et al. TGF-beta receptor-mediated albumin uptake into astrocytes is involved in neocortical epileptogenesis. *Brain* 2007; 130:535–547.
39. Ricci R, Bacci A, Tugnoli V, et al. Metabolic findings on 3T 1H-MR spectroscopy in peritumoral brain edema. *Am J Neuroradiol* 2007; 28:1287–1291.
40. Lyons SA, Chung WJ, Weaver AK, et al. Autocrine glutamate signaling promotes glioma cell invasion. *Cancer Res* 2007; 67:9463–9471.
41. Sontheimer H. A role for glutamate in growth and invasion of primary brain tumors. *J Neurochem* 2008; 105:287–295.
42. Sontheimer H. An unexpected role for ion channels in brain tumor metastasis. *Exp Biol Med* 2008; 233:779–791.
43. Buckingham SC, Campbell SL, Haas BR, et al. Glutamate release by primary brain tumors induces epileptic activity. *Nat Med* 2011;17:1269-1274.
44. Aronica E, Yankaya B, Jansen GH, et al. Iontropic and metabotropic glutamate receptor protein expression in glioneuronal tumours from patients with intractable epilepsy. *Neuropathol Appl Neurobiol* 2001; 27:223–237.
45. Maas S, Patt S, Schrey M, et al. Underediting of glutamate receptor GluR-B mRNA in malignant gliomas. *Proc Natl Acad Sci USA* 2001; 98:14687–14692.
46. Lee MC, Kang JY, Seol MB, et al. Clinical features and epileptogenesis of dysembryoplastic neuroepithelial tumor. *Childs Nerv Syst* 2006; 22:1611–1618.
47. Samadani U, Judkins AR, Akpalu A, et al. Differential cellular gene expression in ganglioglioma. *Epilepsia* 2007; 48:646–653.
48. Aronica E, Boer K, Becker A, et al. Gene expression profile analysis of epilepsy-associated gangliogliomas. *Neuroscience* 2008; 151:272–292.
49. Berntsson SG, Malmer B, Bondy ML, et al. Tumor-associated epilepsy and glioma: are there common genetic pathways? *Acta Oncol* 2009; 48:955–963.
50. Huang L, You G, Jiang T, Li G, Li S, Wang Z. Correlation between tumor-related seizures and molecular genetic profile in 103 Chinese patients with low-grade gliomas: a preliminary study. *J Neurol Sci* 2011;302:63-67.

51. Ben-Ari Y, Dudek FE. Primary and secondary mechanisms of epileptogenesis in the temporal lobe: there is a before and an after. *Epilepsy Curr* 2010;10:118-125.
52. Berger MS, Ghatan S, Haglund MM, Dobbins J, Ojemann GA. Low-grade gliomas associated with intractable epilepsy: seizure outcome utilizing electrocorticography during tumor resection. *J Neurosurg* 1993;79:62-69.
53. Fried I, Kim JH, Spencer DD. Limbic and neocortical gliomas associated with intractable seizures: a distinct clinicopathological group. *Neurosurgery* 1994;34:815-823.
54. Zaatreh MM, Firlik KS, Spencer DD, et al. Temporal lobe tumoral epilepsy: characteristics and predictors of surgical outcome. *Neurology* 2003; 61:636–641.
55. Luyken C, Blümcke I, Fimmers R, et al. The spectrum of long-term epilepsy-associated tumors: long-term seizure and tumor outcome and neurosurgical aspects. *Epilepsia* 2003; 44:822–830.
56. Choi JY, Chang JW, Park YG, et al. A retrospective study of the clinical outcomes and significant variables in the surgical treatment of temporal lobe tumor associated with intractable seizures. *Stereotact Funct Neurosurg* 2004; 82:35–42.
57. Bauer R, Dobesberger J, Unterhofer C, et al. Outcome of adult patients with temporal lobe tumours and medically refractory focal epilepsy. *Acta Neurochir* 2007; 149:1211–1216.
58. Phi JH, Kim SK, Cho BK, et al. Long-term surgical outcomes of temporal lobe epilepsy associated with low-grade brain tumors. *Cancer* 2009; 115:5771–5779.
59. Englot DJ, Berger MS, Barbaro NM, et al. Predictors of seizure freedom after resection of supratentorial low-grade gliomas. A review. *J Neurosurg* 2011;115:240-244.
60. Duffau H. Surgery of low-grade gliomas: towards a 'functional neurooncology'. *Curr Opin Oncol* 2009;21:543-549.
61. Bello L, Fava E, Carrabba G, Papagno C, Gaini SM. Present day's standards in microsurgery of low-grade gliomas. *Adv Tech Stand Neurosurg* 2010;35:113-57.
62. Duffau H, Capelle L. Preferential brain locations of low-grade gliomas. *Cancer* 2004;100:2622-2626.
63. Yordanova YN, Moritz-Gasser S, Duffau H. Awake surgery for WHO Grade II gliomas within “noneloquent” areas in the left dominant hemisphere: toward a “supratotal” resection. Clinical article. *J Neurosurg.* 2011;115:232–239.
64. Blonski M, Taillandier L, Herbet G, et al. Combination of neoadjuvant chemotherapy followed by surgical resection as a new strategy for WHO grade II gliomas: a study of cognitive status and quality of life. *J Neurooncol* 2012;106:353-366.
65. Rudà R, Trevisan E, Soffiatti R. Low-grade gliomas. In: *Handb Clin Neurol* (Grisold W, Soffiatti R, eds), Elsevier, 2012;105:437-450.
66. Englot DJ, Berger MS, Barbaro NM, et al. Factors associated with seizure freedom in the surgical resection of glioneuronal tumors. *Epilepsia* 2012;53:51-57.
67. Yang I, Chang EF, Han SJ, et al. Early surgical intervention in adult patients with ganglioglioma is associated with improved clinical seizure outcomes. *J Clin Neurosci* 2011;18:29-33.
68. Zentner J, Wolf HK, Ostertun B, et al. Gangliogliomas: clinical, radiological, and histopathological findings in 51 patients. *J Neurol Neurosurg Psychiatry* 1994;57:1497-1502.
69. Aronica E, Leenstra S, van Veelen CW, van Rijen PC, Hulsebos TJ, Tersmette AC, Yankaya B, Troost D. Glioneuronal tumors and medically intractable epilepsy: a clinical study with long-term follow-up of seizure outcome after surgery. *Epilepsy Res* 2001;43:179-191.
70. Clusmann H, Schramm J, Kral T, et al. Prognostic factors and outcome after different types of resection for temporal lobe epilepsy. *J Neurosurg* 2002; 97:1131–1141.
71. Lombardi D, Marsh R, de Tribolet N. Low grade glioma in intractable epilepsy: lesionectomy versus epilepsy surgery. *Acta Neurochir Suppl.* 1997;68:70-74.
72. Giulioni M, Rubboli G, Marucci G, et al. Seizure outcome of epilepsy surgery in focal epilepsies associated with temporo-mesial glioneuronal tumors: lesionectomy compared with tailored resection. *J Neurosurg.* 2009;111:1275-1282.
73. Kurzwelly D, Herrlinger U, Simon M. Seizures in patients with low-grade gliomas: incidence, pathogenesis, surgical management, and pharmacotherapy. *Adv Tech Stand Neurosurg* 2010; 35:81–111.

74. Ghareeb F, Duffau H. Intractable epilepsy in paralimbic World Health Organization Grade II gliomas: should the hippocampus be resected when not invaded by the tumor? *J Neurosurg.* 2012;116: 1226–1234.
75. Pilcher WH, Silbergeld DL, Berger MS, et al. Intraoperative electrocorticography during tumor resection: impact on seizure outcome in patients with gangliogliomas. *J Neurosurg.* 1993 Jun;78(6):891-902.
76. Jooma R, Yeh HS, Privitera MD, Gartner M. Lesionectomy versus electrophysiologically guided resection for temporal lobe tumors manifesting with complex partial seizures. *J Neurosurg.* 1995;83:231-236.
77. Sugano H, Shimizu H, Sunaga S. Efficacy of intraoperative electrocorticography for assessing seizure outcomes in intractable epilepsy patients with temporal-lobe-mass lesions. *Seizure* 2007; 16:120–127.
78. Rossi GF, Scerrati M, Roselli R. Epileptogenic cerebral low-grade tumors: effect of interstitial stereotactic irradiation on seizures. *Appl Neurophysiol* 1985; 48:127–132.
79. Warnke PC, Berlis A, Weyerbrock A, et al. Significant reduction of seizure incidence and increase of benzodiazepine receptor density after interstitial radiosurgery in low-grade gliomas. *Acta Neurochir* 1997; 68:90–92. 53
80. Schröttner O, Unger F, Eder HG, et al. Gamma-knife radiosurgery of mesiotemporal tumour epilepsy observations and long-term results. *Acta Neurochir* 2002; 84:49–55.
81. Mathieu D, Kondziolka D, Niranjan A, et al. Gamma knife radiosurgery for refractory epilepsy caused by hypothalamic hamartomas. *Stereotact Funct Neurosurg* 2006; 84:82–87.
82. Kondziolka D, Lunsford LD, Flickinger JC, et al. The application of stereotactic radiosurgery to disorders of the brain. *Neurosurgery* 2008; 62:707–720. Sugano H, Shimizu H, Sunaga S. Efficacy of intraoperative electrocorticography for assessing seizure outcomes in intractable epilepsy patients with temporal-lobe-mass lesions. *Seizure* 2007; 16:120–127.
83. Rogers LR, Morris HH, Lupica K. Effect of cranial irradiation on seizure frequency in adults with low-grade astrocytoma and medically intractable epilepsy. *Neurology* 1993; 43:1599–1601.
84. Rudà R, Trevisan E, Magliola U, et al. Efficacy of radiation therapy on epileptic seizures of grade 2 and 3 gliomas : a retrospective study. *J Clin Oncol* 2011; 29: 2074 (abstract).
85. van den Bent MJ, Afra D, de Witte O, et al; EORTC Radiotherapy and Brain Tumor Groups and the UK Medical Research Council. Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial. *Lancet* 2005; 366:985–990.
86. Mason W, Krol G, De Angelis LM. Low grade oligodendroglioma responds to chemotherapy. *Neurology* 1996; 46:203–207.
87. Soffietti R, Rudà R, Bradac GB, et al. PCV chemotherapy for recurrent oligodendrogliomas and oligoastrocytomas. *Neurosurgery.* 1998;43:1066-1073.
88. Brada M, Viviers L, Abson C, et al. Phase II study of primary temozolomide chemotherapy in patients with WHO grade II gliomas. *Ann Oncol* 2003; 14:1715–1721.
89. Pace A, Vidiri A, Galiè E, et al. Temozolomide chemotherapy for progressive low-grade glioma: clinical benefits and radiological response. *Ann Oncol* 2003; 14:1722–1726.
90. Hoang-Xuan K, Capelle L, Kujas M, et al. Temozolomide as initial treatments for adults with low-grade oligodendrogliomas or oligoastrocytomas and correlation with chromosome 1 p deletions. *J Clin Oncol* 2004; 22:3133–3138.
91. Frenay MP, Fontaine D, Vandebos F, et al. First-line nitrosourea-based chemotherapy in symptomatic nonresectable supratentorial pure low-grade astrocytomas. *Eur J Neurol* 2005;12:685–690.
92. Kaloshi G, Benouaich-Amiel A, Diakite F, et al. Temozolomide for low-grade gliomas: predictive impact of 1p/19q loss on response and outcome. *Neurology* 2007; 68:1831–1836.
93. Lebrun C, Fontaine D, Bourg V, et al. Treatment of newly diagnosed symptomatic pure low-grade oligodendrogliomas with PCV chemotherapy. *Eur J Neurol* 2007; 14:391–398.
94. Taillandier L, Duffau H. Epilepsy and insular grade II gliomas: an interdisciplinary point of view from a retrospective monocentric series of 46 cases. *Neurosurg Focus* 2009; 27:E8.
95. Sherman JH, Moldovan K, Yeoh HK, et al. Impact of temozolomide chemotherapy on seizure frequency in patients with low-grade gliomas. *J Neurosurg* 2011;114:1617-1621.

96. Rudà R, Bertero L, Trevisan E, et al. Phase II trial of dose-dense temozolomide as initial treatment for progressive low-grade oligodendrogial tumors : a multicentric study of the Italian Association of Neuro-Oncology (AINO). *J Clin Oncol*, 2012; 30: 2037 (abstract).
97. Krueger DA, Care MM, Holland K, et al. Everolimus for subependymal giant-cell astrocytomas in tuberous sclerosis. *N Engl J Med* 2010;363:1801-1811.
98. Franz DN. Everolimus: an mTOR inhibitor for the treatment of tuberous sclerosis. *Expert Rev Anticancer Ther* 2011;11:1181-1192.
99. Hildebrand J. Management of epileptic seizures. *Curr Opin Oncol*. 2004;16:314-317.
100. Perry JR, Sawka C. Add-on gabapentin for refractory seizures in patients with brain tumours. *Can J Neurol Sci*. 1996;23:128-131.
101. Striano S, Striano P, Boccella P, Nocerino C, Bilo L. Tiagabine in glial tumors. *Epilepsy Res*. 2002;49:81-85.
102. Wagner GL, Wilms EB, Van Donselaar CA, Vecht Ch J. Levetiracetam: preliminary experience in patients with primary brain tumours. *Seizure*. 2003;12:585-586.
103. Maschio M, Albani F, Baruzzi A, Zarabla A, Dinapoli L, Pace A et al. Levetiracetam therapy in patients with brain tumour and epilepsy. *J Neurooncol*. 2006;80:97-100.
104. Newton HB, Goldlust SA, Pearl D. Retrospective analysis of the efficacy and tolerability of levetiracetam in brain tumor patients. *J Neurooncol*. 2006;78:99-102.
105. Maschio M, Dinapoli L, Zarabla A, Pompili A, Carapella CM, Pace A et al. Outcome and tolerability of topiramate in brain tumor associated epilepsy. *J Neurooncol*. 2008;86:61-70.
106. Novy J, Stupp R, Rossetti AO. Pregabalin in patients with primary brain tumors and seizures: a preliminary observation. *Clin Neurol Neurosurg*. 2009;111:171-173.
107. Rosati A, Buttolo L, Stefini R, Todeschini A, Cenzato M, Padovani A. Efficacy and safety of levetiracetam in patients with glioma: a clinical prospective study. *Arch Neurol*. 2010;67:343-346.
108. Kerrigan S, Grant R. Antiepileptic drugs for treating seizures in adults with brain tumours. *Cochrane Database Syst Rev*. [Review]. 2011;8:CD008586.
109. Maschio M, Dinapoli L, Mingoia M, Sperati F, Pace A, Pompili A et al. Lacosamide as add-on in brain tumor-related epilepsy: preliminary report on efficacy and tolerability. *J Neurol*. 2011;258:2100-2104.
110. Merrell RT, Anderson SK, Meyer FB, Lachance DH. Seizures in patients with glioma treated with phenytoin and levetiracetam. *J Neurosurg*. 2010;113:1176-1181.
111. Lim DA, Tarapore P, Chang E, Burt M, Chakalian L, Barbaro N et al. Safety and feasibility of switching from phenytoin to levetiracetam monotherapy for glioma-related seizure control following craniotomy: a randomized phase II pilot study. *J Neurooncol*. 2009;93:349-354.
112. Vecht CJ, van Breemen M. Optimizing therapy of seizures in patients with brain tumors. *Neurology*. 2006;67:S10-13.
113. Vecht CJ, Wilms EB. Seizures in low- and high-grade gliomas: current management and future outlook. *Expert Rev Anticancer Ther*. 2010;10:663-669.
114. Patsalos PN, Perucca E. Clinically important drug interactions in epilepsy: interactions between antiepileptic drugs and other drugs. *Lancet Neurol*. 2003;2:473-481.
115. Vecht CJ, Wagner GL, Wilms EB. Interactions between antiepileptic and chemotherapeutic drugs. *Lancet Neurol* 2003; 2:404-409.
116. Yap KY, Tay WL, Chui WK, et al. Drug interactions between chemotherapeutic regimens and antiepileptics. *Clin Ther* 2008; 30:1385-1407.
117. Maschio M, Albani F, Jandolo B, et al. Temozolomide treatment does not affect topiramate and oxcarbazepine plasma concentrations in chronically treated patients with brain tumor-related epilepsy. *J Neurooncol* 2008; 90:217-221.
118. Butowski NA, Chang SM. General and neurological complications of targeted therapy. In: *Handb Clin Neurol*. (Grisold W, Soffietti R, eds); Elsevier, 2012;105:937-945.
119. Bourg V, Lebrun C, Chichmanian RM, et al. Nitroso-urea-cisplatin-based chemotherapy associated with valproate: increase of haematologic toxicity. *Ann Oncol* 2001; 12:217-219.
120. Calatuzzolo C, Gelati M, Ciusani E, et al. Expression of drug resistance proteins Pgp, MRP1, MRP3, MRP5 and GST-pi in human glioma. *J Neurooncol* 2005; 74:113-121.

121. Aronica E, Gorter JA, Jansen GH, et al. Expression and cellular distribution of multidrug transporter proteins in two major causes of medically intractable epilepsy; focal cortical dysplasia and glioneuronal tumors. *Neuroscience* 2003; 118:417–429.
122. Bauer B, Hartz AM, Pekcec A, et al. Seizure-induced up-regulation of P-glycoprotein at the blood-brain barrier through glutamate and cyclooxygenase-2 signaling. *Mol Pharmacol* 2008; 73:1444–1453.
123. Löscher W. Drug transporters in the epileptic brain. *Epilepsia* 2007; 48:8–13.
124. Baltés S, Fedrowitz M, Tortos CL, et al. Valproic acid is not a substrate for P-glycoprotein or multidrug resistance proteins 1 and 2 in a number of in vitro and in vivo transport assays. *J Pharmacol Exp Ther.* 2007;320:331–343.
125. Tang R, Faussat AM, Majdak P, et al. Valproic acid inhibits proliferation and induces apoptosis in acute myeloid leukemia cells expressing P-gp and MRP1. *Leukemia.* 2004;18:1246–1251.
126. Glantz Mj, Cole BF, Forsyth PA, et al. Practice parameters: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. *Neurology* 2000; 54:1886–1893.
127. Sirven JI, Wingerchuk DM, Drazkowski JF, et al. Seizures prophylaxis in patients with brain tumors: a meta-analysis. *Mayo Clin Proc* 2004; 79:1489–1494.
128. Tremont-Lukats IW, Ratilal BO, Armstrong T, et al. Antiepileptic drugs for preventing seizures in people with brain tumors. *Cochrane Rev The Cochrane Library* 2009; 1–20 [Wiley].
129. Siomin V, Angelov L, Vogelbaum MA. Results of a survey of neurosurgical practice patterns regarding the prophylactic use of antiepilepsy drugs in patients with brain tumors. *J Neuro-Oncol* 2005; 74:211–215.
130. Mauro AM, Bompreszi C, Morresi S, et al. Prevention of early postoperative seizures in patients with primary brain tumors: preliminary experience with oxcarbazepine. *J Neurooncol* 2007; 81:279–285.
131. Milligan TA, Hurwitz S, Bromfield EM. Efficacy and tolerability of levetiracetam versus phenytoin after supratentorial neurosurgery. *Neurology* 2008; 71:665–669