Seizures in patients with low-grade gliomas – incidence, pathogenesis, surgical management, and pharmacotherapy

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Abstract

Seizures complicate the clinical course of >80% of patients with low-grade gliomas. Patients with some tumor variants almost always have epilepsy. Diffuse low-grade gliomas (LGG) are believed to cause epilepsy through partial deafferentiation of nearby brain cortex (denervation hypersensitivity). Glioneural tumors may interfere with local neurotransmitter levels and are sometimes associated with structural abnormalities of the brain which may produce seizures. The severity of tumor associated epilepsy varies considerably between patients. Some cases may present with a first seizure. Others suffer from long-standing pharmacoresistant epilepsy.

Seizure control rates of >70–80% can be expected after complete tumor resections. Patients with drug-resistant epilepsy require a comprehensive preoperative epileptological work-up which may include the placement of subdural (and intraparenchymal) electrodes or intraoperative electrocorticography (ECoG) for the delineation of extratumoral seizure foci. Partial and subtotal tumor resections are helpful in selected cases, i.e. for gliomas involving the insula.

In one series, 40% of patients presented for surgery with uncontrolled seizures, i.e. medical therapy alone often fails to control tumor-related epilepsy. Use of the newer (second generation) non-enzyme inducing antiepileptic drugs (non-EIAED) is encouraged since they seem to have lesser interactions with other medications (e.g. chemotherapy). Chemotherapy and irradiation may have some minor beneficial effects on the patients' seizure disorder.

Overall 60–70% of patients may experience recurrent epilepsy during long-term follow-up. Recurrent seizures (not infrequently heralding tumor recurrence) after surgery continue to pose significant clinical problems.

Keywords: Low-grade glioma; epilepsy; surgery; medical treatment.

Introduction

Patients with low-grade gliomas (LGG) frequently present with epilepsy. In some patients, a LGG is diagnosed during the work-up for a first time seizure. Indeed, new epileptic seizures, in particular partial seizures, in an adult warrant a thorough neuroradiological work-up including an MRI study. In one study, a tumor was diagnosed in 8% of cases as the underlying cause in patients >15

years [96]. Early diagnosis of a brain tumor will facilitate treatment. Preoperative tumor burden is an important prognostic parameter in patients with LGG [101].

Other patients, e.g. with (para)limbic gliomas will develop medication-refractory epilepsy, and the impact of the seizure disorder on the patients' quality of life may dominate treatment decisions rather than the mere oncological aspects [54, 99]. These patients require carefully designed tumor operations with removal of non-neoplastic brain tissue in addition to the removal of the tumor, i.e. "epilepsy" surgery [10, 19, 122].

Quality of life is an important issue for patients with all types of brain tumors. Neurological and neuropsychiatric impairments caused by the disease are often inevitable. Surgical and non-surgical treatments may inflict additional deficits. Aggressive treatment can result in new functional impairments. The respective risks have to be balanced against their presumed oncological benefits. However, successful treatment of the tumor may also improve her or his quality of life. In particular, surgical removal of the tumor will often cure (or at least ameliorate) the patient's epilepsy [67, 24].

Epileptic seizures are not always benign. Even among patients with epilepsy without an underlying neoplastic condition, there is a considerable excess mortality [51]. Casuistic evidence suggests that seizures rank prominently among the treatable causes of unfavorable outcomes after brain tumor surgery [31]. Early postoperative seizures often indicate some surgical complication such as a hematoma [43]. Late recurrence of seizures or a modification of the seizure pattern in brain tumor patients may herald tumor recurrence [24].

In summary, epilepsy is a major issue for patients with low-grade gliomas and their physicians. For this review we have therefore summarized the available data on the incidence, pathogenesis, and treatment of epilepsy in LGG patients. In particular, we will focus on the surgical treatment and pharmacological management of tumor-related epilepsy.

Tumor-related seizures: semiology and classification

Epilepsy is a chronic disease of the brain characterized by 'an enduring predisposition to generate epileptic seizures' ([39] Definitions by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE)). There is a general consensus that in the neurooncological setting a single epileptic seizure suffices to diagnose epilepsy. By definition, symptomatic tumor-associated epilepsy is a focal epilepsy, and many patients will present with partial seizures. However, secondary generalization is common, and the focal beginning of a seizure may be clinically inapparent and pass so quickly that one often will have the impression of a primary generalized grand mal

epilepsy. In one large study, generalized seizures alone were seen in 33% of patients with LGG presenting with epilepsy, complex and simple partial seizures alone in 16% and 22%, respectively, and more than one seizure type in 29% [24].

Ictal semiology reflects the somatotopic distribution of brain functions. Hence, focal epileptic syndromes can be classified according to their site of origin. In earlier times, focal seizures played an important role in localizing brain tumors. Because of the availability of high quality neuroimaging this is no longer an important clinical issue. Temporal lobe epilepsy (TLE) is characterized by complex partial seizures usually preceded by an aura. Auras may consist of unfocused fear, memory distortions (déjà-vue), and visceral sensations (e.g. epigastric auras). Oral and motor automatisms (e.g. dystonic posturing) are frequent. Secondary generalization is common. TLE can be further subdivided into mesial and lateral (neocortical) TLE based on the precise location of the epileptogenic zone. Complex visual and acoustic hallucinations, and vertigo are more frequently seen in lateral TLE, while epigastric auras and dystonic posturing are more characteristic of mesial TLE [48, 81]. Frontal lobe epilepsy presents – depending on the exact origin – with contralateral, single or serial, clonic convulsions, which may spread as a Jacksonian march. Impairment of consciousness, speech arrest and complex automatisms (e.g. body rocking) may also occur. If the epileptic focus is located close to the occipital pole or in its vicinity, simple (flashes or scotomas) or complex (e.g. micropsy or macropsy) visual and even scenic hallucinations may occur.

Drug-resistant epilepsy is common in patients with LGG. In the series reported by Chang *et al.* [24] 132/332 (39.8%) patients suffered from pharmacoresistant seizures. Pharmacoresistance can be defined as failure to control epilepsy by at least two first-line antiepileptic drugs, with a seizure frequency of at least one per month for 18 months [82]. Distinguishing between patients presenting with a first or with occasional seizures vs. drug-resistant epilepsy has important implications. Surgical treatment strategies, and the biology and/or histology of the tumor will differ between these patient groups (see below). However, sometimes the distinction between controllable and drug-resistant epilepsy in tumor patients may become blurred. Some LGG patients are diagnosed following their first seizure and will undergo surgery before the seizure disorder has proven pharmacoresistant.

From a clinical point of view, it is also important to distinguish between early and late postoperative seizures. Seizures shortly after surgery often herald a surgical complication such as a hemorrhage [43]. Newly occuring seizures in a seizure-free patient, seizures with a new semiology, or a worsening of seizure frequency are often seen in the context of tumor recurrence [24].

Tumor-related seizures: the role of histology and tumor location

Histology

The incidence of seizures varies widely with tumor histology and location reflecting the respective growth pattern and the susceptibility of the brain structures involved. Astrocytomas and oligodendroglial tumors WHO grade II account for the majority of LGG. Seizures occur in 50 to >90% of patients with WHO grade II astrocytomas and oligodendroglial tumors [73, 24]. Chang and colleagues studied a series of 129 astrocytomas, 109 oligoastrocytomas, and 95 oligodendrogliomas. Eighty-nine percent of the patients with oligodendroglial tumors, and 68% of astrocytoma cases had preoperative seizures [24]. Oligodendrogliomas are said to cause seizures more frequently because of their more cortical location as compared to astrocytomas which tend to primarily involve white matter tracts [61].

Patients with certain rare intrinsic brain tumors almost exclusively present with seizures. Glioneural tumors are a prime example. Dysembryoplastic neuroepithelial tumors (DNTs) most often affect the temporal lobe, but also grow in other parts of the brain including the brainstem [75]. Only very few patients with DNTs do not have epilepsy [84]. Similarly, the majority of gangliogliomas occur in the temporal lobe. In a series of 184 gangliogliomas from our institution, 79% temporal tumors were observed. Only 6 patients (3%) presented with symptoms other than seizures [68]. Clinical presentation is an important prognostic factor in ganglioglioma. In a study of 4 recurrent/progressive WHO grade I gangliogliomas, 21 gangliogliomas with atypical histological characteristics (WHO grade II) and 5 anaplastic gangliogliomas (WHO grade III), progression-free and overall survival was worst for patients without seizures [69].

Supratentorial pilocytic astrocytomas also frequently cause seizures. In a series of 44 adult cases with pilocytic astrocytomas, 19/20 (95%) patients with lobar tumors presented with epilepsy [103]. The series reported by Brown *et al.* [20] included 5 patients with seizures out of a total of 13 cases with lobar tumors (38%). Pilocytic astrocytomas of the deep midline structures, brainstem and cerebellum usually present with symptoms other than seizures [38, 103]. Fouladi *et al.* reported seizures in 8/12 of their (pediatric) patients with cerebral pleomorphic xanthoastrocytomas (PXA) [40]. Subependymal giant cell astrocytomas (SEGA) are assigned to the WHO grade I. These tumors typically grow in the wall of the lateral ventricles and present with hydrocephalus and seizures. SEGA may complicate the clinical course of 6–14% of patients with tuberous sclerosis (tuberous sclerosis complex, TSC). Patients with apparently spontaneous SEGA may develop further signs of TSC during follow-up [2, 97].

The recently revised WHO classification [18] includes several other rare glioma and glioneural tumor subtypes assigned to the WHO grades I and II

which present with seizures, i.e. angiocentric glioma WHO grade I [60, 115], papillary glioneuronal tumor WHO grade I [56], glioneuronal tumor with neuropil-like islands WHO grade II–III [108], and (extraventricular) neurocytomas [17]. Finally, there are some data to indicate that long-standing epilepsy may be the clinical hallmark of some LGG entities which have not yet been comprehensively characterized. Such tumors may ('isomorphic astrocytoma', [11, 93]) or may not [5] display specific histomorphological features.

Tumor location

The location of the tumor may be an even more important determinant of tumor-associated epilepsy than its histological composition. Clinical experience with tumor patients and patients with penetrating and non-penetrating head trauma suggests that certain areas of the brain, in particular the cortex near the central sulcus, the hippocampus and others parts of the (para)limbic system, and the frontal and temporal lobe in general are more likely to generate seizures than others [36]. Accordingly, Liigant *et al.* [61] reported an association between tumor location in the frontal, frontoparietal, temporal and frontotemporal region and the occurrence of seizures in a series of 165 brain tumor patients with epilepsy.

Chang *et al.* [24] studied 332 diffuse supratentorial LGG. Frontal lobe involvement was significantly associated with preoperative epilepsy in the univariate analysis, while a subcortical location with tumor growth in the deep midline structures was less likely to result in seizures. However, multivariate analysis revealed only tumor histology (oligodendroglial tumor) and involvement of midline structures as significant independent positive and negative predictors of preoperative epilepsy, respectively [24]. Duffau *et al.* reported seizures in 39/40 patients with fronto-precentral, 8/8 rolandic, and 6/7 parieto-postcentral LGG [32].

Seizures are also very common in temporal lobe tumors. Many of these patients suffer from drug-resistant epilepsy. In the series reported by Chang *et al.* 86% of 111 patients with LGG of the temporal lobe presented with epilepsy [24]. Intractable epilepsy is particularly often seen in tumors which involve the temporo-mesial structures. In a recent series of 235 operations for temporo-medio-basal tumors (24% malignant gliomas, 76% gliomas and glioneural tumors WHO grades I and II) from the authors' institution, 91% of patients had seizures. Drug-resistant epilepsy was diagnosed in 72% of cases [94]. This is not to say that seizures are infrequent in patients with purely lateral (neocortical) temporal lobe tumors. Luyken *et al.* reported a series of 229 neuroepithelial, supratentorial hemispheric tumors presenting with intractable epilepsy of more than 2 years duration. This series included 113 (55%) cases with temporo-mesial but also 57 (28%) patients with temporo-lateral tumors [67].

Not only involvement of the mesial aspect of the temporal lobe, but also tumor growth in the paralimbic and limbic system in general will often cause epilepsy. Thirty-four of 36 patients (94%) with WHO grade I and II paralimbic (insular) gliomas operated at the authors' institution presented with epilepsy (Fig. 1; [99]). Similarly, all of the 42 patients with insular low-grade gliomas reported by Duffau *et al.* suffered from preoperative epilepsy [34]. Yasargil observed seizures in 50/60 (83%) benign intrinsic insular tumors. Twenty-one of Yasargil's 24 patients with benign tumors of the cingulate gyrus (88%) had epilepsy [119].

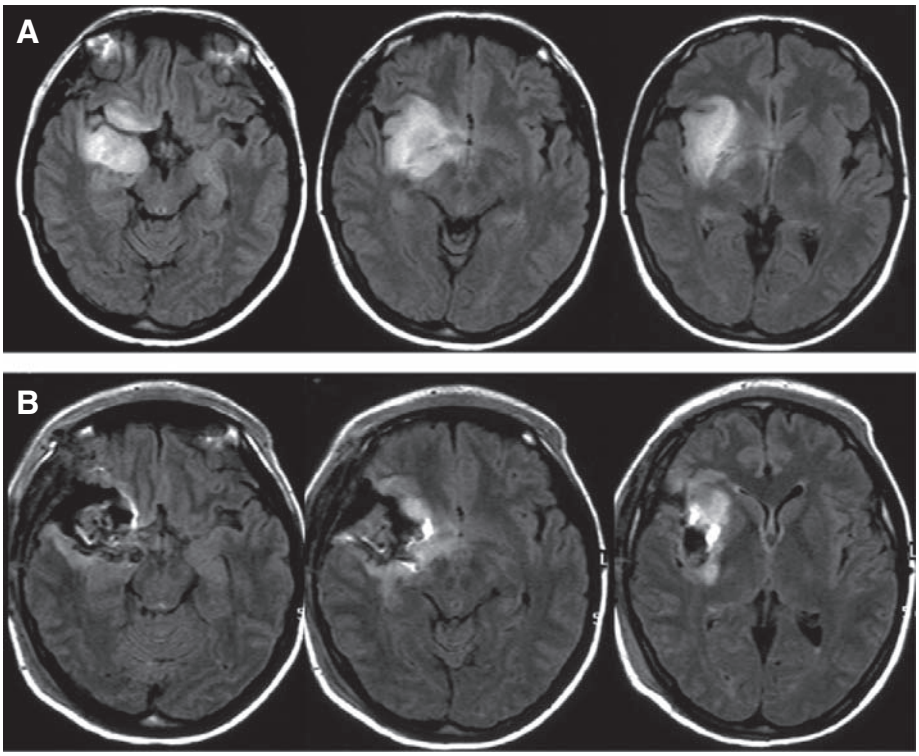

Fig. 1. A) Preoperative FLAIR images of a right paralimbic (insular) astrocytoma WHO grade II. The 40 year old female patient presented with a history of two generalized seizures and multiple complex partial seizures. The tumor involves the uncus but not the hippocampus (Yasargil type 5A). There is also minor tumor growth in the frontoorbital area. B) Postoperative FLAIR images depict a $>70\%$ resection of the tumor. There was no postoperative neurological deficit. At the most recent (three year) follow-up there was no tumor progression. The patient reported occasional auras but no complex partial or generalized seizures. Her antiepileptic medication is currently switched from carbamazepine to levetiracetam because of protracted leucopenia (see Table 1 for side effects of common anticonvulsants). (Dr. Neuloh, Dept. of Neurosurgery, Univ. of Bonn, helped with the preparation of this figure)

However, the high overall incidence of epilepsy in patients with lobar low-grade glioma together with the relatively high number of tumors affecting the frontal, temporal and insular lobe [32] limits somewhat the clinical implications of regional differences in the epileptogenic potential of the various cortical brain areas. In addition, there are clinically important correlations between tumor location and histology. As already pointed out above the majority of glioneural tumors occur in the temporal lobe. Duffau and Capelle have provided some evidence that diffuse low grade astrocytomas and oligodendrogliomas may have preferential locations, too. In contrast to malignant gliomas, low-grade gliomas tend to grow in secondary functional areas close to but rarely directly within primary eloquent parts of the brain [33].

LGG of the deep midline structures, the brainstem and the cerebellum rarely cause seizures [24]. Seizures in such patients often reflect treatment complications such as a cortical bleeding following a stereotactic biopsy of a tumor of the basal ganglia. Some of these patients have undergone placement of a ventriculoperitoneal or ventriculoatrial shunt. Seizures in shunt patients may occur in the context of a shunt infection or malfunction. However, this risk is generally overestimated [55]. In a large French series the risk to develop a seizure in a formerly seizure-free patient with a shunt malfunction but without obvious clinical signs of increased intracranial pressure was only 3.5% [14].

Intraoperative and postoperative seizures

Intraoperative and early postoperative seizures

Seizures occuring during surgery are sometimes dramatic events accompanied by impressive brain swelling. This usually raises the possibility of a disastrous complication somewhere remote from the surgical site. Treatment includes irrigation of the surgical field with cold saline or Ringer's lactate [89]. Intraoperative mapping and monitoring may induce seizures. Controlling seizures in patients undergoing awake craniotomies may be more of a problem, since barbiturates and relaxation can not be used in patients not operated under general anesthesia. Fortunately, these are rare events. In the series reported by Szelény *et al.* [104], only one of 63 patients (1.6%) presenting with symptomatic epilepsy, and only one of 66 patients without a history of preoperative epilepsy (1.5%) experienced a stimulation-induced seizure.

The overall incidence of perioperative seizures in glioma patients is not high. An 8% perioperative seizure rate has been reported for 499 glioma WHO grade III and IV patients enrolled in the Glioma Outcome Project. These authors prospectively recorded all complications occurring within the first 21 days following surgery [25]. Using a 30 day observation period, Sawaya *et al.* [90] noted a 2.5% seizure rate in series of 400 craniotomies

including 40 low-grade and 166 high-grade gliomas. Somewhat higher numbers have been reported in some older series [43]. Of note, seizures rank prominently among the treatable causes of unfavorable outcomes after brain tumor surgery [31].

Seizures in the immediate postoperative period should always alert the neurosurgeon to the possibility of a surgical complication. Fukamachi *et al.* diagnosed 9 hemorrhages and 4 infarctions in 44 patients presenting with a seizure within the first 48 h following craniotomy [43]. However, inadequate anti-convulsant levels are probably the most important risk factor for early postoperative seizures [58]. At the authors' institution, a CT scan is urgently obtained in all non-epileptic patients experiencing a seizure within the first 24–48 h following surgery.

Late postoperative seizures

Recurrent seizures or a change in seizure frequency or semiology in a glioma patient will usually prompt an MR investigation to rule out tumor progression. Several authors have reported significant correlations between seizure recurrence and tumor progression. Hwang *et al.* investigated tumor-associated epilepsy in 101 astrocytomas WHO grades II–IV. Tumor recurrence or malignant progression was diagnosed in as many as 10 of 18 patients with late onset seizures [50]. In the large series of LGG reported by Chang *et al.*, time of tumor progression could be ascertained for 79 of the 161 patients who were seizure-free at the 6-month follow-up. Forty-one of these 79 cases had a seizure prior to progression. On the other hand, recurrent seizures do not always herald tumor progression. In the same series, 73 patients had experienced seizure recurrence at eighteen months, however, tumor progression was noted in only 11 cases [24].

Overall seizure outcomes after surgery for intrinsic brain tumors may not be as stable as generally thought, in particular after incomplete resections. In the study by Chang *et al.*, 73 of 161 patients (45%) who were seizure-free at the 6 months follow-up, developed recurrent seizures by 18 months. A complete tumor resection had been achieved in 48%, and 37% of the cases had presented with uncontrolled seizures [24]. Nevertheless, long-term seizure outcomes can be excellent even in patients presenting with drug-resistant epilepsy [67]. These authors reported a $>80\%$ seizure control rate after 10 years of follow-up.

Pathogenesis of tumor-related seizures

The etiology of tumor-related seizures is probably multifactorial. Though various mechanisms of epileptogenesis in brain tumor patients have been

suggested, the specific events leading to tumor-related epileptic activity are still not fully understood [109]. There is evidence that the mechanisms of seizure generation vary for different tumor types [112], and this may also explain the differences in seizure frequency between tumor entities. LGG and other slow-growing tumors have been suggested to produce an epileptogenic milieu by partial deafferentation of cortical brain regions, thus causing denervation hypersensitivity [35, 112, 118]. Developmental tumors consist of well-differentiated cells, which are able to release neurotransmitters and other modulators involved in epileptogenesis [118]. They may be associated with structural abnormalities of the cortex, which are likely to cause epileptic activity. In contrast, high-grade brain tumors, such as glioblastoma multiforme, and metastasis are assumed to induce seizures via tissue damage or mass effect due to necrosis or tumor bleeding and edema, respectively [8, 85], leading to impaired vascularisation and ischemic changes in the surrounding tissue [79].

Secondary epileptogenesis is a phenomenon predominantly seen in younger patients with slow-growing, low-grade tumors of the temporal lobe, and implies, that the tumor induces distant, actively discharging epileptogenic foci [71, 45, 66, 109]. Certain morphologic changes in the peritumoral brain tissue, such as persistent neurons in the white matter, inefficient neuronal migration [47], changes in synaptic vesicles, and alterations in glial gap-junction coupling are also believed to contribute to seizure generation [8, 113].

Voltage-gated ion channels controlling cell excitability and synaptic processes are involved in the generation of seizures. Hence, changes in the local concentrations of gamma amino butyric acid (GABA) and glutamate are thought to affect tumor-related epileptogenesis through imbalances between inhibitory and excitatory factors [6, 8]. Ion and amino acid level changes, neuroreceptor disturbances as well as enzymatic changes and immune-mediated mechanisms all have been shown to play a role in tumor-related epilepsy [8]. Hypoxia in neoplasms and adjacent regions due to an imbalance between blood perfusion and an increased metabolism may lead to changes of the pH in the peritumoral brain tissue with consecutive cell damage and, therefore, increased neuronal excitability [8].

Surgical treatment for tumor-related seizures

Epilepsy in low-grade glioma (LGG) patients: a good indication for surgical treatment

Surgery for LGG is still somewhat controversial, and no prospective study specifically investigating the role of the tumor resection has been conducted. However, the extent of resection has been shown to be a major prognostic

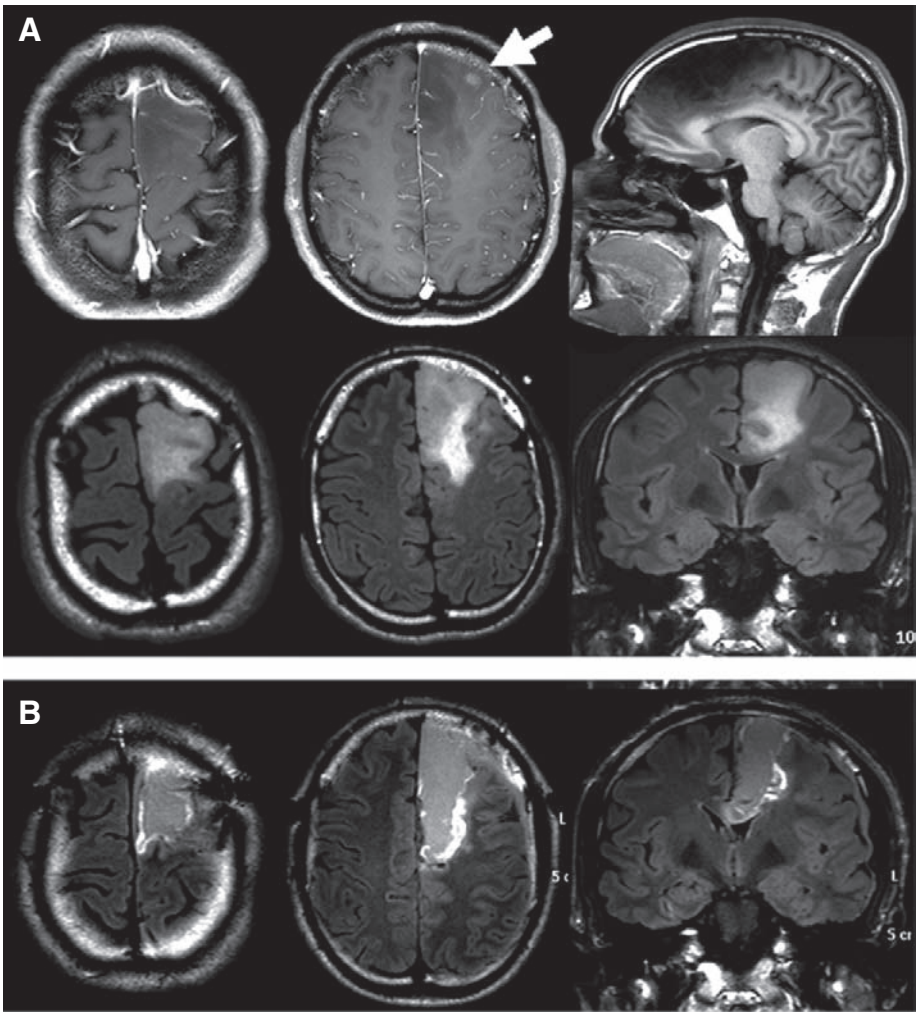

Fig. 2. A) Preoperative T1 weighted (after administration of contrast medium, *upper row*) and FLAIR (*lower row*) MR scans depicting a diffuse glioma of the left mesial frontal lobe (i.e. the superior frontal gyrus and the cingulum) which involves the SMA (supplementary motor area). The tumor was diagnosed in a 24 year old male following two generalized seizures. There is focal contrast enhancement (*arrow*). Nevertheless, the histological diagnosis was astrocytoma WHO grade II. B) Postoperative FLAIR images showing a complete tumor resection. The tumor was removed under continuous electrophysiological monitoring. As expected, there was a transient hemiparesis and aphasia (SMA syndrome). One year after the surgery, the patient has only minimal speech difficulties. He had two auras but no further generalized seizures in the year after the surgery and is treated with lamotrigine by his neurologist

factor in many and in particular in the more recent studies [59, 101]. In contrast, there is little disagreement that LGG patients with seizures will very often experience a substantial relief from their epilepsy. Recurrent seizures have a major negative impact on the patients' quality of life [54]. Age-related mortality is increased two- to threefold in epileptics. At least some cases are caused by seizures and not by the underlying disease [51]. Finally, there is some evidence to suggest that epileptics will benefit from early treatment and respond with better seizure control [66, 71]. Together, these are three good reasons to recommend surgery to a patient with a LGG presenting with epilepsy.

Epilepsy control after "tumor surgery"

A radical tumor resection, i.e. the complete removal of the tumor as defined by imaging criteria, offers a good chance for seizure control in many patients with LGG (Fig. 2). In the series reported by Chang *et al.*, 74/83 (89%) patients were seizure-free at 6 months following a gross total resection as compared to only 94/165 cases (57%) after a biopsy or a subtotal tumor removal [24]. A gross-total resection has been identified as a positive predictor of seizure control in many other case series as well. Packer *et al.* have described a cohort of 60 children with seizures and cortical low grade intrinsic brain tumors. Forty-seven of their patients underwent a total or near-total tumor resection, 45 of which (96%) became seizure-free [78]. Surgical removal of temporal lobe tumors presenting with epilepsy will result in postoperative seizure control in 65 to 77% [26, 121].

Patients with tumor-related epilepsy may sometimes derive substantial benefits even from incomplete tumor resections. As mentioned above, 57% of the LGG patients with a subtotal resection or biopsy in the study by Chang *et al.* were seizure-free during short-time follow-up [24]. In a series of 101 operations for insular gliomas from the authors' institution removal of $>90\%$ of the tumor mass was achieved in 42%, and a 70–90% resection in 51% of cases. 83 surgeries were performed in patients with seizures. Epileptological one-year outcomes were available in 55 cases with more than one preoperative seizure: 42 patients (76%) were seizure-free or experienced only auras or simple partial seizures (Engel class I) (Fig. 1; [99]).

"Epilepsy surgery" for tumor-related drug-resistant epilepsy

Conceptually, successful surgical treatment for epilepsy requires the complete removal of the epileptogenic zone (i.e., the cortical area indispensable for the generation of epileptic seizures). In brain tumor cases the epileptogenic zone typically consists of the tumor and variable amounts of surrounding tissue. The epileptogenic zone does not extend substantially beyond the borders of the tumor in most cases with occasional seizures. Hence, as summarized above, a

gross-total tumor resection is quite appropriate for the majority of patients with LGG and tumor-associated epilepsy.

In contrast, the epileptogenic zone may include significant extra-tumoral cortical areas in patients with drug-resistant tumor-related epilepsy. This is nicely illustrated by the experience with stereotactic lesionectomies for focal intractable epilepsy. The term 'lesionectomy' refers to the resection of pathological tissue only (the 'lesion') in the context of surgical treatment for epilepsy. A stereotactically guided procedure is probably the purest form of lesionectomy. Stereotactic lesionectomies resulted only in a 56% seizure control rate in the series of 23 patients with drug-resistant partial epilepsy reported by Cascino *et al.* [22].

Indeed, considerable clinical evidence suggests that a more comprehensive approach aiming at the identification and removal of the epileptogenic zone (i.e. 'epilepsy surgery') will result in improved epilepsy outcomes in patients with tumor-associated intractable epilepsy. Seizure outcomes after lesionectomy vs. 'epilepsy surgery' for patients with intractable epilepsy have been compared by several authors. Rossi *et al.* [88] reported a 66% seizure control rate after lesionectomies and 79% following epilepsy surgery for 28 temporal and 20 extratemporal WHO grade I–II gliomas. Jooma *et al.* [52] analyzed their experience with 30 temporal lobe tumors presenting with complex partial seizures. Sixteen patients underwent only a lesionectomy, and 14 patients a resection of the lesion with electroencephalographic delineation and excision of the presumptive epileptogenic zone. Seizure control was achieved in 13 (93%) of the latter patients, while only three (19%) of the lesionectomy only patients became seizure-free. A further eight of these cases underwent a temporal lobectomy as a second procedure, 5 (63%) of which became seizure-free. Lombardi *et al.* analyzed 22 cases of LGG associated with intractable epilepsy including 8 temporo-lateral (extra-hippocampal) and 7 temporo-mesial tumors (with invasion of the amygdalo-hippocampal complex). Only 4/8 (50%) patients with temporo-lateral tumors were seizure-free after a lesionectomy. However, in 2 of the 4 patients with an unfavorable seizure outcome, a second pathology ('dual pathology', tumor and hippocampal atrophy) was present which was not surgically addressed. Both patients became seizure-free after a temporal lobectomy [63]. The experience detailed in the latter two studies underlines the important role of the temporo-mesial structures in many cases of tumor-associated temporal lobe epilepsy. One of the central issues in surgery for temporal lobe tumors presenting with intractable epilepsy is to determine if the amygdalo-hippocampal complex is part of the epileptogenic zone or not.

Surgical treatment for tumor-associated frontal lobe pharmacoresistant epilepsy poses specific problems. Frontal lobe tumors often grow close to the motor and/or language cortex. This often limits the possible extent of

resection. Zaatreh *et al.* operated on 37 patients with drug-resistant tumor-associated frontal lobe epilepsy including 28 cases with intrinsic brain tumors. A gross-total resection was perfomed in 27 patients. Only thirteen (35%) patients were seizure-free or had only auras (Engel class I) during longterm follow-up [120]. Experience at the authors' institution has been somewhat more rewarding. In a series of 68 operations for intractable frontal lobe epilepsy, 54% of all patients, and 58% of the 34 tumor cases had an Engel class I outcome. Of note, the epileptogenic zone was electrophysiologically defined in 81%. If the epileptogenic zone included eloquent cortex (25%), a partial resection and MST (multiple subpial transections) were perfomed [92].

"Epilepsy surgery" for tumor-related drug-resistant epilepsy: how to define the epileptogenic zone

Performing an extended lesionectomy rather than a lesionectomy alone, i.e. resecting not only the tumor but in addition a rim of 0.5–1 cm of surrounding cortex will remove the epileptogenic zone in many patients with tumor-related intractable epilepsy. Similarly, the resection of a temporo-mesial tumor can be extended to include the amygdalo-hippocampal complex (or parts thereof). This simple strategy has been quite successful with respect to epilepsy control [91, 28]. Good seizure control rates have also been reported after mostly extended lesionectomies for focal epilepsies in pediatric patients [15].

A more aggressive approach to tumor-associated epilepsy in LGG patients involves the electrophysiological identification (Fig. 3) and resection of extratumoral seizure foci. If questions remain after the non-invasive work-up, two basic surgical options exist which help with the delineation of the epileptogenic zone: intraoperative electrocorticography (ECoG) and extraoperative mapping after implantation of depth and subdural strip and grid electrodes. Intraoperative ECoG (Fig. 3A) allows for the intraoperative identification of the irritative zone, i.e. the cortical area capable of producing interictal electrographic spikes. Disadvantages include the influence of anesthesia and short recording times. Intraparenchymal (depth) and cortical surface (subdural) electrodes can be used to record not only interictal electrical activity but also genuine seizures, i.e. help to delineate the seizure onset zone. Subdural electrodes can also be used to map eloquent cortical areas (Fig. 3B). However, two operations (electrode placement and tumor resection) are required, and the implantation of subdural and intraparenchymal electrodes carries a small but significant complication rate, e.g. the development of subdural hematomas necessitating emergency evacuation. Of note, neither intraoperative ECoG nor the use of subdural/intraparenchymal electrodes followed by extraoperative mapping allows to always precisely delineate the epileptogenic zone. The epileptogenic zone is operationally defined by the absence of seizures after its

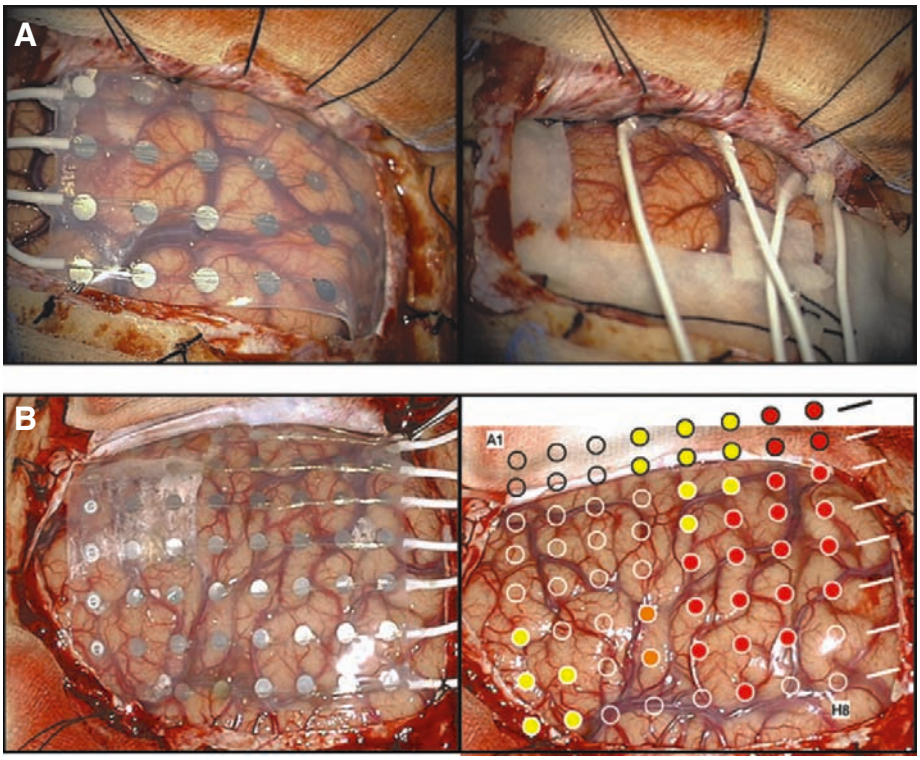

Fig. 3. A) Intraoperative electrocorticography of the right temporal lobe. A grid electrode (*left*) and four temporo-basal strip electrodes (*right*) are used sequentially to record interictal electrographic spikes in order to map the *irritative zone*. The planned resection is indicated by cottonoids. B) Placement (*left*) of a large frontal grid electrode covering the eloquent areas of the dominant frontal lobe. The craniotomy is closed and the electrodes allow for the recording of actual seizures occurring in the days following surgery. These recordings help with the delineation of the *seizure onset zone*. In addition, ''extraoperative'' electrophysiological mapping makes the functional identification of the precentral gyrus (*red* and *orange* dots) and the cortical language areas (*yellow* dots) possible. Resective epilepsy surgery aims at removing the *epileptogenic zone*. Of note, both the *irritative* as well as the *seizure onset zones* are approximations of but do not equal the *epileptogenic zone*. (The photographs used for this figure were provided by Dr. Clusmann, Dept. of Neurosurgery, and Prof. Elger, Dept. of Epileptology, Univ. of Bonn, Germany)

removal, and not by the production of interictal electrographic spikes or the onset of seizures [95].

Intraoperative electrocorticography (ECoG) has been used by many groups to improve seizure outcomes in patients with intrinsic brain tumors and epilepsy. Berger *et al.* employed ECoG as an adjunct during surgery for 45 low-grade tumors with drug-resistant epilepsy. Forty-one of their patients

(91%) were seizure-free after surgery (with and without medication) [10]. Britton *et al.* treated 51 patients with medication-refractory focal epilepsy and LGG. Seventeen patients had a lesionectomy and in 34 cases an additional corticectomy was performed after ECoG. Sixty-six percent of patients were seizure-free during follow-up [19].

At the authors' institution, both intraoperative ECoG and implantation of subdural and depth electrodes have been used to optimize seizure outcomes in patients with drug-resistant epilepsy and (mostly) low-grade intrinsic brain tumors. In a series of 146 operations, intraoperative ECoG was employed in 42 cases (29%), and extraoperative mapping in 40 patients (27%). Of the 124 patients with a follow-up exceeding 6 months, 71% became seizure-free [122]. However, the number of patients undergoing intraoperative or invasive extraoperative electrophysiological mapping has declined in more recent years. In particular, growing experience and improved neuroimaging have resulted in a lesser number of invasive evaluations for tumor-associated temporal lobe epilepsy. Schramm *et al.* [91] reported 62 cases with drug-resistant neocortical temporal lobe epilepsy including 35 patients with tumors. An extended lesionectomy without electrophysiological mapping was performed in 50 cases. 89% of the tumor cases became seizure-free (or had only isolated, non-debilitating seizures = Engel class I). Clusmann *et al.* [28] described 74 patients with mesial temporal lobe epilepsy (including 55 tumor cases) undergoing limited temporal lobe resections. Engel class I outcomes were seen in 78%. Only 24% of the patients had an invasive preoperative evaluation. Patients with extratemporal intractable epilepsy are still commonly evaluated using subdural grid electrodes and sometimes intraoperative ECoG. Of note, in these cases the need to obtain a reliable map of functional cortical areas influences the decision to proceed with the invasive evaluation just as much as epileptological concerns (Fig. 3).

Effects of cranial irradiation and chemotherapy on tumor-related epilepsy

Radiotherapy

While the beneficial impact of surgery on a seizure disorder in brain tumor patients is well recognized, there are also some data indicative of a reduction of seizure frequency by radio- and/or chemotherapy. However, data on this issue are rare and mainly stem from a few small series. In a retrospective analysis including 5 patients with low-grade astrocytoma Rogers *et al.* [86] observed a reduction of seizure frequency of more than 75% with a follow-up time up to 8.2 years from the first date of irradiation. Similar results were found by another group [23], and Rossi *et al.* [87] observed that stereotactic interstitial irradiation had a positive effect on epilepsy in patients with unre-

sectable gliomas. Improved seizure control after irradiation may be due to a reduction in tumor size. Further theories include damage to epileptogenic neurons in the surrounding of the tumor or alterations of local metabolic effects by radiotherapy [86]. However, cerebral irradiation may also lead to a transient increase in seizure frequency as a result of secondary complications such as edema, bleeding or necrosis. Moreover, the risk of late-onset neurotoxicity with seizures as part of the clinical problem has to be considered before initiating brain irradiation, especially in younger patients with a presumably better prognosis.

Chemotherapy

There is some preliminary evidence that pharmacological antitumor treatment might be associated with improved seizure control. Chemotherapy with the alkylating agent temozolomide was reported to reduce seizure frequency in 50% to 60% of patients with progressive LGG [77]. Similar data were presented in another clinical trial: 54% of patients with symptomatic epilepsy due to WHO grade II gliomas experienced a reduction in seizure frequency [16]. Besides temozolomide nitrosourea-based chemotherapeutic regimens, such as PCV (procarbazine, CCNU, vincristine) chemotherapy play a role in the treatment of LGG. In a small clinical trial all ten patients treated with a nitrosourea-based regimen had clinical improvement with a reduction of seizure frequency, and 60% of the patients even became seizure-free [42]. Further clinical studies of much larger patient series seem warranted to substantiate this effect of chemotherapy on tumor-related epilepsy.

Pharmacological treatment

Who should be treated with anticonvulsants, and how long?

Medical treatment for tumor-related epilepsy is not satisfactory so far, and data derived from prospective, placebo-controlled studies are scarce. Anticonvulsive therapy is generally recommended after occurrence of a first and single seizure in neurooncological patients [109, 116]. In contrast to previous data [41], Wick *et al.* [117] found in a retrospective analysis of the seizure history of 107 glioma patients undergoing surgery, that preoperative seizures were not a predictor for the occurrence of postoperative epilepsy. These data may justify withholding treatment with AEDs in LGG patients after an uneventful gross total resection of the tumor and weaken the indication for long-term anticonvulsive treatment in cases with pre-operative seizures.

There is no general indication for prophylactic antiepileptic therapy in glioma patients. Primary prophylactic treatment with phenytoin, phenobarbital or valproic acid in patients with primary brain tumors, meningiomas, or brain

metastases was found to be ineffective in two meta-analyses (AAN standard, [46, 100]). The use of anticonvulsants in patients who are undergoing surgery for a brain tumor is also not generally indicated. Primary prophylaxis with phenytoin in patients with cerebral metastasis and supratentorial primary brain tumors was not effective in two randomized clinical trials [29, 30]. However, prophylactic preoperative treatment with anticonvulsants may be helpful in some cases because of casuistic evidence pointing to perioperative seizures as a major treatable cause of adverse outcomes after brain tumor surgery [31].

According to a consensus statement published by the Quality Standards Subcommittee of the American Academy of Neurology [46] primary prophylaxis with antiepileptic drugs (AEDs) should not be used, anticonvulsants discontinued in patients who have never experienced seizures, and – following brain surgery – it is recommended to discontinue AEDs after one week in patients without a history of seizures. Patients who presented with a single seizure, but remained seizure-free after surgery may be kept on antiepileptics for 3 months [117], but there are no randomized trials on this issue so that treatment may be discontinued even after a shorter time interval. Patients with persistent seizures after surgery usually need long-term anticonvulsive treatment, and the decision for drug withdrawal should be made on an individual basis if the tumor is stable, the patient has not experienced seizures for at least one year, and the EEG does not show abnormal discharges suggestive of an increased predisposition to seizure generation.

At the authors' institution, no routine preoperative antiepileptic prophylaxis is prescribed. Patients assumed to be at a particularly high risk for complications following a seizure are given anticonvulsants. A typical example would be a large frontotemporal convexity meningioma in a septuagenarian. Of note, patients with presumed LGG rarely – if ever – fall into this category. Patients presenting with a first seizure are not routinely treated. Antiepileptics are used in cases with more than one preoperative seizure. The antiepileptic medication is discontinued after three months, if the patient remains seizure-free and has had a complete resection. Patients undergoing epilepsy surgery are typically maintained on their preoperative anticonvulsant medication for two years.

Common antiepileptic drugs (AEDs) and recommendations for first line therapy

Only a few prospective, randomized studies specifically dedicated to the medical treatment of seizures in neurooncological patients have been published. Simply following treatment guidelines for symptomatic localisation-related epilepsy [53] can not be recommended for patients with brain tumors without carefully taking into account pharmacokinetic and pharma-

codynamic mechanisms, potential drug interactions and interactions with concomitantly administered chemotherapy, as well as possible side effects and co-morbidity.

Enzyme-inducing AEDs (EIAEDs) such as the first-generation anticonvulsants carbamazepine, phenytoin and phenobarbital are no longer considered first-choice anticonvulsive drugs for tumor-related seizures because they may lead to accelerated metabolism, reduced plasma concentrations and thus lower anticancer activity of simultaneously given chemotherapeutics via an influence on the cytochrome P450 enzyme system of the liver. The increasing use of chemotherapy for recurrent and progressive LGG renders this more than a theoretical concern [16, 42, 77]. Various chemotherapeutics are substrates of the cytochrome P450 enzyme system, and EIAEDs have been proved to reduce the effects of taxanes, methotrexate, irinotecan and nitrosureas [4, 111]. Conversely, antineoplastic agents can lead to accelerated metabolism and thus diminished plasma concentrations of EIAEDs with the consequence of impaired seizure control. This has been reported for antineoplastics such as cisplatin, vincristin or methotrexate if given together with carbamazepine, phenytoin or valproic acid.

In a retrospective analysis of patients with glioblastoma multiforme treated with adjuvant chemotherapy (most patients receiving CCNU) after surgery and irradiation, patients who were given EIAEDs (80% carbamazepine) had a significantly shorter overall survival than patients on non-EIAEDs (80% valproic acid), 10.8 versus 13.9 months, respectively [74]. This effect could be due to an accelerated metabolism of CCNU in patients receiving EIAEDs and/or a potential intrinsic antitumor effect of valproic acid. Valproic acid inhibits histone deacetylase, leading to growth arrest and apoptosis of malignant cells [37, 62]. Being an enzyme inhibitor, valproic acid may decelerate the metabolism of concomitantly administered antineoplastic drugs and – by raising their plasma concentrations – increase their activity but also toxic effects [13]. The use of add-on anticonvulsant medication might be necessary since monotherapy with valproic acid often does not achieve sufficient seizure control [112].

On the basis of the interactions and characteristics of the classic EIAEDs and valproic acid outlined above, it seems reasonable to consider the new (second generation) anticonvulsants with a reduced potential for interactions and side effects such as levetiracetam, gabapentin, pregabalin, and zonisamide, as well as lamotrigine and topiramate for the primary therapy of patients with brain tumors (Table 1; [12, 27, 102]). No relevant interactions with chemotherapy or other simultaneously given drugs have been reported for gabapentin and levetiracetam. Some drugs have already been established as first- or second-line antiepileptic agents for the treatment of neurooncological patients. Phenytoin and benzodiazepines may still be used for the treatment and prevention of early

Table 1. *First-generation and new (second-generation) antiepileptic drugs (AEDs)*

Generic name (trade names)	Dose range (mg/day)*/ monotherapy	Therapeutic serum level (μg/ml)†	i.v.	Common and relevant side effects	Pharmacokinetic interactions
Levetiracetam (Keppra®)	1000–3000	10–80‡	+	Sedation and fatigue (rare), irritability, nervousness and other mood changes	Probably none
Gabapentin (Neurontin®)	900–3600	‡	–	Sedation and fatigue, possibly cognitive problems	Probably none
Pregabalin (Lyrica®)	300–600**	‡	–	Vertigo, fatigue, weight gain, irritability, incoordination	Probably none
Zonisamide (Zonegran®)	300–500**	15–40‡	–	Anorexia, irritability, depression, ataxia, dizziness, diplopia, cognitive impairment, kidney stones	No enzyme induction (but co-administration with cytochrome P450 inducers or inhibitors may change its pharmacokinetic profile; [7]
Lamotrigine (Lamictal®)	100–600	2–15‡	–	Allergic skin reactions, Stevens-Johnson syndrome, tremor, ataxia, insomnia (rare)	Possibly weak enzyme induction
Topiramate (Topamax®)	50–200	7–20‡	–	Dizziness, paresthesia, weight loss, fatigue, sedation, kidney stones, neurocognitive side effects	Possibly weak enzyme induction
Oxcarbazepine (Trileptal®, Timox®)	600–2400	10–35	–	Similar to carbamazepine but less frequent, except: >1% hyponatriemia	CYP450 induction
Carbamazepine (Tegretal®, Timonil®)	400–2000	4–9	–	Hyponatriemia, dizziness, fatigue, nausea, ataxia, skin reactions, elevated liver enzymes, leuco- and thrombopenia	CYP450 induction

Table 1. (*continued*)

Phenytoin (Phenhydan®, Zentropil®)	200–350	5–20	+	Elevation of liver enzymes, dizziness, nausea, ataxia, headache, allergic skin reactions, gingival hyperplasia, cerebellar atrophy, cardial arrhythmia and conduction defects	CYP450 induction
Phenobarbital (Luminal®)	50–300	10–40	+	Drowsiness, headache, allergic skin reactions, irritability and aggressive mood changes, constipation	CYP450 induction
Primidone (Liskantin®, Mylepsinum®)	500–1500	5–15	–	Tiredness, headache, allergy; also see phenobarbital	CYP450 induction
Valproic acid (Ergenyl®, Orfiril®)	1200–2400	40–100	+	Hepatotoxicity, weight gain, tremor, alopecia, edema, teratogenicity, thrombopenia, coagulopathy (?)	Enzyme inhibition

* Dose rates must be adapted to concomitant medication with respect to possible pharmacokinetic und -dynamic interactions.
** Only add-on therapy (zonisamide: licensed for use as adjunctive therapy for partial seizures in adults).
† Varying in different laboratories; here: according to the standards of the Neuropharmacological Laboratory, Department of Epileptology, University of Bonn.
‡ Not assessed routinely; indications as follows: survey of compliance, occurrence of side effects or signs of intoxication, insufficient control of epilepsy or relapse after a period of satisfactory seizure control, polypharmacotherapy with anticonvulsants and concomitant drugs – to assess possible interactions, severe comorbidity and metabolic disturbances with e.g. malabsorption.

postoperative seizures, if the clinical scenario necessitates an immediate therapeutic effect.

Lamotrigine may be used for tumor-related epilepsy, but has the disadvantage of a protracted dosage schedule and may cause severe skin reactions such as Stevens-Johnson syndrome. Pregabalin and zonisamide are licensed for use as add-on anticonvulsants and may also become important in the neurooncological setting as they do not exhibit relevant interactions with chemotherapeutics and other drugs. In addition, zonisamide acts through a combination of multiple mechanisms that are potentially complementary to other AEDs [7, 57]. However, while some authors report overall good tolerability of zonisamide with the majority of side effects being mild-to-moderate [7], others observed limiting adverse events leading to discontinuation of therapy (Table 1).

The authors prefer monotherapy with levetiracetam as first-line anticonvulsive treatment for patients who will presumably need chemotherapy or long-term treatment with corticosteroids when anticonvulsant therapy is required. A randomized trial on levetiracetam monotherapy for treatment of newly diagnosed partial epilepsy found that levetiracetam was as effective as monotherapy with carbamazepine and associated with fewer side effects [9, 109]. Levetiracetam can be administered intravenously if necessary, and therapeutic dose rates can be achieved within 3 days [70, 72]. The efficacy of levetiracetam – both as monotherapy and add-on agent – appears to be higher than that of gabapentin [110, 76]. In addition, treatment with levetiracetam does not seem to be affected by multidrug efflux transporters such as P-glycoprotein (PGP) or multidrug resistance proteins (MRPs) located at the level of the blood–brain barrier [83]. While these multidrug transporters are thought to actively restrict the penetration of many AEDs into the brain, Potschka *et al.* [83] showed that inhibition of these multidrug transporters does not alter the blood-brain barrier penetration of levetiracetam in an animal model. These authors concluded that levetiracetam is not a substrate for these transporters.

Toxicity and side-effects of anticonvulsant drugs

AED side effects occur more frequently in patients with brain tumors than in the general population of patients with epilepsy [46, 116] This was also observed in a cross-sectional study on 195 patients with LGG mainly addressing neurocognitive sequelae in the course of the disease [107]. Frequent and important side effects of selected AEDs are detailed in Table 1. Generally, neurocognitive deficits, myelosuppression, liver dysfunction with elevated liver enzymes, and dermatological reactions may occur with anticonvulsant therapy, leading to discontinuation or modification of treatment in approximately 20% to 40% of patients. Bone-marrow toxicity necessitating a change of the anticonvulsant

therapy is seen in 3%. Hemostatic and coagulation disorders have been associated with the use of valproic acid [1, 44], however, this has not been substantiated in other studies [3, 117]. At the authors' institution, pre-treatment with valproic acid is not regarded as a contraindication against elective surgery. These patients undergo a careful preoperative hemostaseological evaluation and any (potential) deficits are corrected using von-Willebrand factor/factor VIII, vasopressin, and thrombocyte concentrates as indicated.

Second line therapy and mechanisms of pharmacoresistance

Anticonvulsant treatment of tumor associated epilepsy is often not very effective. One hundred and thirty-two patients (40%) in the unselected low-grade glioma series reported by Chang *et al.* had uncontrolled seizures before surgery [24]. One should expect that over time 60–70% of patients continue to have seizures despite treatment with AEDs. Hildebrand *et al.* analysed a series of 234 primary brain tumors including 93 patients with low-grade gliomas (40%) for epileptic seizures during follow-up after surgery. They noted at least one seizure within two months in two-thirds of their patients, 88% of which were treated with antiepileptic drugs [49]. Chang *et al.* reported 108 patients with persistent and 73 with recurrent seizures at 18 months among 269 LGG patients (67%) presenting with epilepsy [24].

Several anticonvulsants have been recommended as add-on anticonvulsive therapy, if first-line therapy fails [70, 80, 98, 114]. Combining valproic acid and levetiracetam may be a good first choice, if monotherapy with either drug is insufficient. Levetiracetam and gabapentin both can be used as add-on agents if monotherapy with other antiepileptics, such as carbamazepine, lamotrigine, oxcarbazepine, phenytoin or topiramate, has turned out to be ineffective. Pregabaline and zonisamide may also be used for add-on treatment. Various clinical trials with add-on levetiracetam showed a substantial reduction of seizure frequency [70, 72, 114].

Pharmacological treatment may fail because of a loss of receptor sensitivity, tumor growth, overactivity of AED-resistance pathways [105] or because of pharmacokinetic and pharmacodynamic interactions with concomitantly administered medications and chemotherapy. Genes encoding different MRPs have been shown to be up-regulated in human epilepsy and brain tumors. These proteins are constitutively expressed in human endothelial cells and contribute to the function of the blood–brain barrier. Up-regulation of these genes may limit the access of drugs to the brain. This appears to be one important cause of pharmacoresistance of seizures associated with brain tumors [21, 64]. Whereas there is evidence that carbamazepine, phenytoin and phenobarbital as well as lamotrigine and topiramate are substrates for multidrug resistance protein-1 (MRP1) [64], levetiracetam does not seem to

be affected by MRP1 expression or other multidrug resistance proteins (see above). It has been suggested that valproic acid might even reduce the expression of MRP1 via its histone deacetylase-inhibiting effects [106].

Key facts and conclusion

- Seizures complicate the clinical course of >80% of patients with LGG. Medical therapy alone will frequently fail to control symptomatic epilepsy in LGG patients. In contrast, surgery will often control tumor-associated epilepsy. Irradiation and chemotherapy may have some minor beneficial effects on the patients' seizure disorder.
- Seizure control in patients with drug-resistant epilepsy requires 'epilepsy surgery' rather than a simple gross total tumor resection, i.e. the removal of epileptogenic brain tissue in addition to the tumor.
- Enzyme-inducing antiepileptic drugs (EIAEDs, i.e. carbamazepine, phenytoin, and phenobarbital) are no longer first choice AEDs for tumor-related seizures. Use of the newer (second generation) non-enzyme inducing antiepileptic drugs (non-EIAEDs), such as levetiracetam, gabapentin, pregabalin, zonisamide, as well as lamotrigine and topiramate, is encouraged since they do not interfere with other medications including chemotherapy.
- There is no general indication for prophylactic antiepileptic therapy in LGG patients. Patients who present with a single seizure may be treated with antiepileptics for up to 3 months. In cases with persistent seizures after surgery long-term anticonvulsive treatment is usually necessary. After surgery for drug-resistant epilepsy anticonvulsive medication is usually continued for two years.
- AED withdrawal can be considered if the tumor is stable, the patient has not experienced seizures for at least one year, and the EEG does not show abnormal discharges suggestive of an increased predisposition to seizure generation.
- Recurrent seizures after surgery (not infrequently heralding tumor recurrence) continue to pose significant clinical problems.

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