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# Seizures in Children with Brain Tumours – Epidemiology, Significance, Management, and Outcomes

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## 1. Introduction

Cancer is the most frequently diagnosed disease-related cause of death among children and adolescents [1], and malignancies involving the brain are collectively the most common solid tumour [2, 3]. They are also either first or second in incidence overall (second only to leukaemia) in the United States (USA) [1, 4,7], Canada [8], and Mexico [9]. The *American Brain Tumour Association* has estimated that approximately 4,200 American children younger than age 20 would be diagnosed with a primary brain tumour in the year 2012, of whom three in four would be under the age of 15 years [10]. However, the overall prognosis for brain malignancies is much better in children than in adults, with up to half of paediatric brain cancer patients surviving long-term [11]. The reason for this enhanced survival in youths is that children and adolescents are much more likely than adults to have low-grade astrocytomas, in particular pilocytic astrocytomas and other low-grade gliomas that are almost never fatal and often cured, depending upon their location and surgical accessibility, rather than the grade III and IV astrocytomas that account for the majority of tumours among adults [12-14].

Long-term survival, even in the setting of cure, is not without problems, however, with empirical evidence accumulating that paediatric brain cancer survivors continue to suffer from significant morbidity [15-20] and, sometimes, early death [15]. Among the more common long-term sequelae of brain cancer and brain cancer treatment in children are seizures, which can be quite disabling and, at times, life-threatening in themselves [15, 21-30]. In one study, seizures were the number one predictor of disability in long-term brain cancer survivors [24, 25]. Seizures even increase a paediatric survivor's risk of suicide into adulthood [31]. In addition,

there is a subset of children, up to 50% [32], whose low-grade brain cancer presents as seizures [26, 32-42]. Though the vast majority of epileptogenic tumours are supratentorial, some are not, especially among children in whom infratentorial tumours generally comprise the majority [43, 44], and in less typical locations like the thalamus and hypothalamus [38, 45-47]. Among thalamic tumours, for example, up to one third of paediatric patients present with seizures [38]. As such, and because even low-grade gliomas can nonetheless be infiltrative into high-function brain tissue [19, 48-50], while some of these lesions are totally resectable, others are not [51-54]. This creates dilemmas as to how aggressive to be, and therefore how much risk to take in their resection [55]. As well, the return of seizures at some distant time post-operatively may indicate tumour growth or relapse [28, 30, 56-66], transformation into a more aggressive lesion [28, 60, 65, 67, 68], or even the emergence of a secondary (e.g., radiation-induced) tumour [64].

Why seizures occur in patients with brain tumours is not entirely clear [27, 69-71], and several conjectures have been made, including alterations in regional metabolism and pH, immunologic activity, disordered neuronal function, altered vascular supply and permeability, the release of altered tumoral amino acids, proteins and enzymes, and abnormal protein transport and binding to receptors [27, 44, 69, 71-74]. Even genetic predispositions for tumour-related seizures have been postulated [71, 75]. A recent excellent review of current theories and empirical evidence on the pathogenesis of tumour-related epilepsy has been published by You et al. [74] Discussing the relative merits of each theory is a paper in itself, and beyond the scope of the current review.

Interestingly, tumour size has a somewhat paradoxical relationship with seizure occurrence, in that, though the opposite is true of low-grade lesions, high-grade gliomas that present with seizures tend to be smaller than those that present with other symptoms [76]. Moreover, high-grade lesions that present with seizures tend to have a better prognosis than lesions of the same size that present otherwise [77]. What this suggests is that the aggressiveness of the tumour might have an effect upon seizure development. This being said, low-grade lesions comprise the majority of epileptogenic tumours, both in children and adults [78]; and some tumour types — like gangliogliomas and dysembryoplastic neuroepithelial tumours (DNET) — are more likely to induce seizures than others [28].

In this chapter, we will thoroughly review the literature on seizures in paediatric brain cancer patients, looking at them (1) as a presenting symptom; (2) in the early tumour management/peri-operative period; and (3) long-term. Specific questions to be addressed in each of these sections are: How common are they? What is their history? How do they impact patients' lives, both short-and long-term, and in terms of management and prognosis? How do they effect management of the underlying tumour? How are seizures managed themselves? As much as possible, these questions will be answered by examining empirical evidence across a number of studies to provide, if not definitive answers, at least conclusions that are supported by published research.

## 2. Seizures as a presenting symptom of a brain tumour

### 2.1. How seizures present

A brain tumour is ultimately discovered in between one and three percent of children who present with new-onset seizures [40, 42], though a slightly higher percentage has been reported in children presenting with partial versus generalized seizures [79], and percentages as high as 20% have been reported in children undergoing epilepsy surgery [80]. From the reverse perspective, somewhere between 10 and 50% of brain tumours present with seizures as a symptom [69, 74, 81-83], and sometimes as the only symptom [32, 41, 84-86], with supratentorial and especially temporal lesions the most likely to be epileptogenic [44, 66, 78, 86-88]. In one study that compared children with supra- and infratentorial tumours, for example, among those with supratentorial lesions, 42% experienced vomiting as their first symptom, followed by seizures in 37%, and headache in 31% [43]. Meanwhile, 62% of children with an infratentorial lesion experienced headaches as their first symptom, with vomiting and ataxia accounting for most of the remainder, and seizures not observed in a single case.

Because children are more likely than adults to have infra-versus supratentorial lesions, the percentage of children presenting with seizures may be somewhat less than among adults, closer to the 10-20% than the 30-50% range [51, 89, 90], though 50% or more has been reported in some series [32, 35]. As in adults, of these epileptic tumours, the vast majority are supratentorial. For example, in their series of 157 children presenting to the hospital with brain tumour-related seizures, of mean age 3.3 years, Khan et al. found that 81% of the tumours were supratentorial and just 19% within the posterior fossa [82]. Meanwhile, Ianelli et al. reported that 80% of their 37 paediatric patients presenting with a temporal lobe malignancy had seizures as a presenting symptom [86]. Another excellent study on new-onset seizures presenting in children with brain cancers was published by Shady et al. [32] who analyzed 98 paediatric brain tumour patients and found that 50% percent of the children had seizures as part of their presentation, and 30% as their only presenting phenomenon; complex (55%) and simple (28%) partial seizures were the most common types, accounting for more than three quarters of all cases. Pre-operative electroencephalography (EEG) accurately lateralized to the tumour side in 88% of the cases and to the correct lobe in 56%. In addition, tumours involving cerebral cortex were much more likely than non-cortical lesions to present with seizures (59% vs. 15% of patients, respectively), with temporal and frontal lobe lesions exhibiting the highest incidence of seizures. Moreover, whereas 88% of gangliogliomas and 86% of oligoastrocytomas were associated with seizures, seizures were noted in just 21% of the patients with an anaplastic astrocytoma. Finally, as described elsewhere [32, 77], patients with seizures at presentation had a better prognosis than those without ( $p=0.02$ ) [32].

Virtually every possible tumour type has been reported presenting as seizures, especially low-grade gliomas [27, 30, 32, 34, 37, 39, 70-72, 75, 76, 78, 91-93] and glioneuronal tumours like ganglioglioma and dysembryoplastic neuroepithelial tumour [28, 44, 62, 73, 88, 89, 91, 94, 95]; but including oligodendroglioma [77, 96, 97], cortical ependymoma [98], medulloblastoma

[47], subependymal giant cell astrocytoma (SEGA) [99], meningioma [10]<sup>0</sup>, thalamic and cerebellar glioma [38, 46], and a variety of atypical, systemic and metastatic tumours, like primary meningeal osteosarcoma [84], acute lymphoblastic leukemia [101], anaplastic large cell lymphoma [102], neuroblastoma [103], melanoma [104], various sarcomas [105, 106], Ewing's sarcoma [107], malignant germ cell tumours [108], and others [16, 109].

There is no stereotypical seizure presenting as an early symptom of a brain tumour. Early seizures may be generalized, simple partial, complex partial, or mixed, depending upon the tumour's size, location, level of aggressiveness, and other factors [24, 26, 27, 33, 34, 37, 70, 74, 77, 82, 87, 110-115]. This being said, among children, seizures as a presenting symptom of brain tumour are most commonly complex or simple partial, versus generalized, with complex partial seizures generally accounting for from 50% to as high as 85% of all new-onset seizures [32, 63, 69, 86, 115-117]. The lone series in which this was not true was that reported by Hirsch et al., in which complex and simple partial seizures together only accounted for half of all cases [118]. The percentages generally reported for children and adolescents are somewhat different than for adults, in whom tumour-associated seizures tend to be more evenly distributed across the four most typical seizure types [58]. Other atypical and, therefore, less well recognized forms of seizure have been described in children as well, including gelastic seizures, characterized by uncontrolled fits of inappropriate laughter [45], tics and Tourette-like symptoms [119], and sympathetic storms in a 7-year old with a midbrain glioma [120]. In addition, especially in the paediatric population, tumors may arise in the setting of a variety of familial syndromes such as neurofibromatosis types 1 [121] and 2 [122], and tuberous sclerosis [123]. Seizures in these conditions are often blong-standing, frequent, and intractable because of the numerous non-neoplastic lesions that can involve the CNS [55, 124, 125]. In such patients, the diagnosis of a new neoplastic lesion can be especially challenging [124, 126].

The diagnosis of brain tumour does not always quickly follow the onset of seizures. In one study reported by Ibrahim et al., for example, the time from seizure onset to tumour diagnosis among ten children presenting with seizures ranged from two weeks to two years, averaging six months [37]. A wide range of opinions and practices exist regarding how aggressive to pursue diagnostic imaging in children presenting with seizures [36, 41, 51, 79, 80, 100, 127-133]. For example, in one series of eighteen patients between the ages of 1 month and 13 years who presented with seizures and were discovered to have DNETs between January 1992 and December 2004, the preoperative evaluation included magnetic resonance (MR) imaging and interictal scalp electro-encephalography (EEG) in all patients, but functional MR imaging also was performed in eight patients, video monitoring with scalp EEG during seizures in 12 patients, interictal single-photon emission computerized tomography (SPECT) scanning in one patient, and ictal SPECT scanning in two patients [132]. Meanwhile, in their 2010 review of eleven clinical trials for anti-epileptic drugs (AEDs) conducted over the preceding two years, Jansky et al. noted that none of the trials required MRI as part of the patient enrollment protocol [128]. Increasingly, with advances in imaging and the recognition that the resection of epileptogenic lesions is both safe and effective for many patients, there seems to be growing opinion that the initial work-up of new-onset non-febrile seizures in children should include

both an EEG and MRI, despite the likelihood that the majority of imaging studies will be either normal or inconclusive [134, 135]. As discussed in the next section, mounting evidence suggests that new-onset seizures in the setting of a tumour, and conversely, tumours in the setting of new-onset seizures both have therapeutic and prognostic implications.

## 2.2. Implications of brain-tumour induced seizures

Having a child's brain tumour present as seizures adds therapeutic complexity with respect to how the patient is initially managed, since peri-operative control of seizures is obviously considered of extreme clinical importance. The type of seizure a patient has also may have prognostic significance, both in terms of patient survival [65, 136] and how easily the seizures are controlled with anti-epilepsy drugs (AED), both peri-operatively and long-term. How well AEDs work, in turn, may have implications relating to how aggressive surgical resection should be.

Although no reliable data have been published for children, adults who present with seizures as their sole symptom tend to have less aggressive or advanced lesions than those who present with symptoms or signs of increased intracranial pressure like papilloedema, headaches [65], neurological or cognitive deficits [65, 136]. Although this intrinsically makes sense — the fewer the symptoms, the less aggressive or advanced the disease — extrapolating these findings to children must be done with caution, because a disproportionate number of paediatric lesions tend to be brainstem tumours that, though usually low-grade and non-epileptogenic, often are non-resectable because of their location and proximity to function-rich neural tissue [2, 3, 137-139]. Nonetheless, especially among supratentorial lesions, it makes sense that having seizures present before all other symptoms develop is a hopeful prognostic sign, given that low-grade gliomas and other so-called benign lesions tend to be associated with much higher seizure rates than high-grade lesions [32, 87, 91, 113, 140, 141].

Having seizures in the presence of a tumour has implications with respect to management of the seizures as well, in that studies have shown that such seizures tend to be more resistant to AEDs than idiopathic seizures [133, 142]. This appears to be especially true for patients who present with a history of numerous seizures [142]. This likelihood of *drug resistance*, which has been formally defined as “*the failure of adequate trials of two tolerated, appropriately-chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom*” [143], may play a role in determining the aggressiveness of surgery for tumour resection. For example, given the clear superiority of epilepsy surgery over medical management alone, in terms of achieving freedom from seizures in patients with intractable seizures (65% vs. 8% in one relatively recent meta-analysis [144]), a decision might be made to pursue more aggressive resection in a patient with repeated new-onset seizures upon initial work-up of seizures and diagnosis of their brain tumour, versus the patient who presents with a single seizure prior to tumour detection. Moreover, for many epileptogenic lesions, surgical resection often leads to either complete resolution of seizures, sometimes without the need for continued AEDs, or to a marked reduction in their frequency, as will be elaborated upon next.

### 2.3. General principles of management

How tumor-induced seizures are managed largely depends upon the aggressiveness and location, and therefore, the prognosis of the underlying tumour. In patients with invariably terminal forms of cancer, including primary brain neoplasms like glioblastoma multiforme (GBM), and metastatic spread to brain, the goal usually is to prolong life over months to, at most, a few years, while preserving as high a quality of life as possible. In both adult and paediatric patients with high-grade astrocytomas like GBM, even partial resection of terminal lesions has been shown both to prolong life and reduce the frequency and severity of seizures [145-147]. Clearly, such surgery needs to be performed as soon after diagnosis of the lesion as possible to have any effect upon outcome. Such is not the case in many patients with low-grade tumours like stage I and II gliomas and gangliogliomas, in whom progression of the tumour may be so slow as to be virtually undetectable, and patients can live for years without apparent disease progression, so that any decision to surgically remove the offending lesion may be delayed for years [58, 93, 148, 149]. This being said, there has been increasing emphasis on surgically resecting low-grade tumours early in the course of disease [131] for a multiplicity of reasons. Among these reasons are that anywhere from 20% to roughly one third of low-grade gliomas (LGG) fail to respond to anti-epileptic medications [72, 150], and many that do respond require more than a single AED [150], placing patients, and especially children, at risk for long-term drug toxicities [23, 24, 59, 71, 151-153]. Among the various documented toxicities of AEDs are wide-ranging adverse effects on cognitive function [23, 153], which already may be impaired because of the tumour itself and the radiation therapy sometimes administered to treat it [18, 20, 154-156]. Moreover, surgical resection of LGG has been shown to enhance long-term survival [19] and to significantly improve the likelihood of seizure control [27, 70].

Though the data are not definitive, there is some evidence suggesting that, among the various seizure types, partial seizures, either simple or complex, may be less likely to respond to anti-epileptic drugs than generalized or mixed seizures [93, 157, 158]. This resistance may be noted initially, so that seizure control is never achieved; but it also may develop over time, so that seizure control is lost and never regained [158, 159]. In such patients, therefore, there may even be an increased incentive to pursue surgical resection of the tumour+/-any adjacent epileptogenic foci, if the lesion can be accessed with no undue risk.

Several studies have shown that radical removal of an epileptogenic brain tumour is a strong, and likely the strongest, predictor of seizure freedom [127]. However, additional predictors include the type of seizure, the histopathology of the tumour, the age of the patient at the time of surgery, and the duration of epilepsy [127]. Among the various tumour histologies, tumours that are non-resectable due to infiltration, like high-grade astrocytomas, can be problematic over the patient's relatively brief period of survival [160]. However, as stated earlier, such high-grade lesions tend to be less often epileptogenic than their low-grade counterparts [32, 87, 91, 113, 140, 141]. In long-term brain cancer survivors, glioneuronal tumours, and particularly low-grade gliomas, gangliogliomas and dysembryoplastic neuroepithelial tumours (DNETs), often produce quite drug-resistant epilepsy in children, so that complete surgical resection of the tumour is typically considered the primary focus of treatment [28, 61-63, 88, 94, 116, 132].

In such patients, post-operative seizure-freedom rates often approach or exceed 80% [35, 48, 51, 58, 66, 86, 88, 90, 93, 115, 157, 161-169].

Traditionally, there has been some concern about being too aggressive with younger children with brain tumours, because of the risk of long-term adverse effects on neurological development, the risk of secondary neoplasms, and other neurological sequelae [155]. That such risks exist is certainly true of radiation therapy [18, 20, 64, 153-156], but it also is true of surgery [170]. However, recent studies have shown that surgery to resect epileptogenic brain tumours is both effective and safe for the vast majority of infants and toddlers [35, 55, 171]. In one large survey, for example, data were collected retrospectively on 116 patients less than 3-years old from eight centers across Canada from January 1987 to September 2005 who had undergone epilepsy surgery [171]. Among the various seizure aetiologies were malformations of cortical development (n=57), tumours (22), Sturge-Weber syndrome (19), and infarcts (8), with 10 cases either of unknown or some other cause. Seizure onset was in the first year of life in 82%, and the mean age at the time of the initial surgery was 15.8 months (range: 1-35 months). Second surgeries were performed in 27 patients, with six patients requiring a third surgical procedure. Among the initial 116 procedures performed were 40 hemispheric operations, 33 cortical resections, 35 lesionectomies, 7 temporal lobectomies, and one callosotomy. Of the 151 operations, including the 27 second and six third procedures, only one resulted in a surgery-related death. The most common surgical complications were infection, in 17 patients, and aseptic meningitis in 13. Of 107 patients assessed more than one year postoperatively, 72 (67.3%) were seizure free (Engel I), 15(14%) had experienced at least a 90% reduction in seizures (Engel II), and 12 had at least a 50% reduction (Engel III), with only eight exhibiting no benefit (Engel IV). Moreover, 55.3% of the children exhibited signs of improved development post-operatively [171].

Consequently, regardless of patient age, the focus for most patients with low-grade lesions has become, whenever possible without the undue risk of peri-operative death or long-term adverse neurological sequelae, to attempt total or at least subtotal tumor resection earlier rather than later in the course of disease. Debate rages, however, as to how aggressive to be achieving this goal, whether or not resecting the lesion alone is enough, and what intra-operative technologies to use to aid in identifying tumour margins and other epileptogenic foci. Moreover, not all patients will be eligible for surgery and will have to rely on non-neurosurgical treatments alone, most notably anti-epileptic drugs (AEDs) and radiation therapy. The next section briefly discusses the benefits, risks and utilization of AEDs both prior to and in lieu of surgery.

### **3. Anti-Epileptic Drugs (AEDs)**

An extensive review paper could be written discussing the various advantages and disadvantages, indications and contra-indications, and drug-drug interactions that exist for the extensive list of anti-epileptic drugs that now are available for use in patients with brain tumour-induced epilepsy, all of which is beyond the scope of the current review. Here, we

briefly describe the roles of AEDs, both in prophylaxis against and control of tumour-induced seizures, some of the risks of prolonged use, and at least the theoretical advantages of the new class of non-enzyme inducing drugs.

### 3.1. AEDs for seizure prophylaxis

In three recent surveys of neurosurgeons, including one survey specifically of members of the *American Association of Neurologic Surgeons* (AANS), the majority (up to 70%) of respondents reported prophylactically initiating AEDs in brain tumour patients who had not yet experienced a seizure [172-174]. This practice of prescribing AEDs prophylactically in brain tumour patients with no seizure history persists, even though empirical evidence addressing this practice is inconclusive at best [78, 81, 127, 140, 172]. Moreover, many authors and the most current *American Association of Neurology* practice parameters argue against it [113, 140, 172, 175, 176]. The argument of AED detractors is that both meta-analyses published since 2000 to address this issue failed to provide sufficient evidence to promote their prophylactic use in brain-tumour patients without seizures [173, 177]. The first meta-analysis, published in 2000 by Glantz et al. [173], analyzed 12 studies, of which four were randomized controlled trials and eight were considered to be “well-designed observational studies with concurrent controls”, sufficient to be classified as class II evidence. Not one of these twelve studies demonstrated a statistical advantage of the AED being studied (phenytoin, depakote, or phenobarbital) over placebo [173]. The second, somewhat more stringent meta-analysis, published in 2004 by Sirven et al [177], only included five RCTs, assessing the prophylactic use of either phenobarbital, phenytoin, or valproic acid. Of the five trials, four identified no statistical benefit of AED use for peri-operative seizure prophylaxis. The one exception was a 1983 study published by North et al [178], in which not only patients with brain tumours, but patients who had undergone craniotomies for aneurisms and head injuries were included. A closer, empirical look at these data reveals no advantage at all when brain tumours are considered alone: seizures occurred in 9/42 on phenytoin, and in 5/39 on placebo (OR=1.11, 95% CI=0.58, 2.12). Further considering just those patients with glial tumours (versus meningiomas, sellar tumours, and metastases), seizures occurred in three of 16 on phenytoin versus just one of 16 on placebo (1.15; 0.42, 3.19) [178]. Overall meta-analysis across the five RCT confirmed the lack of any AED benefit at both one week (OR, 0.91; 95% confidence interval [CI], 0.45-1.83) and six months (OR, 1.01; 95% CI, 0.51-1.98) of follow-up. The AEDs also exhibited no effect on seizure prevention for specific tumours, including primary glial tumors (OR, 3.46; 95% CI, 0.32-37.47), cerebral metastases (OR, 2.50; 95% CI, 0.25-24.72), and meningiomas (OR, 0.62; 95% CI, 0.10-3.85) [177].

More recently, in a review published in 2011, Kargiotis et al. non-statistically examined published evidence on more currently-used AED, including the newer non-enzyme inducing drugs, and concluded that, among patients with either brain metastases or primary brain tumors who have never experienced seizures, prophylactic anticonvulsant treatment might be justified, but only for up to six months postoperatively after surgical excision of the cerebral tumour, since most of these patients will never experience seizures, and the anti-epileptic drugs may cause toxicity and adverse interactions with chemotherapeutic treatments admin-

istered to control the neoplasm itself [109]. For such prophylaxis, the authors argued that newer antiepileptic drugs like levetiracetam and oxcarbazepine are preferable to older agents like phenytoin and carbamazepine [109]. To date, however, no hard evidence supports any of these recommendations, and certainly not in children.

In a study by Hardesty et al., only 7.4% of 223 paediatric patients with brain tumours but no history of seizures experienced even a single seizure during their surgical admission, even though only 4.4% of patients had been started on a prophylactic AED [179]. This percentage is similar to the 8.0% observed among those on placebo in a controlled study in which 127 patients awaiting brain tumour surgery, ranging in age from 16 to 84 years, were randomized to receive either phenytoin 15mg/kg intravenously in the operating room, followed by 100 mg three times daily, either by mouth or intravenously, for seven days or placebo [180]. Thereafter, the dose of each was tapered. The 30-day incidence of seizures actually was higher in the phenytoin group (10.0%) than in controls (8.0%), albeit not statistically so. Moreover, the rate of complications was 18.0% versus 0% in the treatment versus placebo group, respectively ( $p < 0.001$ ).

In the Hardesty study on youths [179], dependent factors associated with peri-operative seizures included a supratentorial tumour, patient age less than two years, and the presence of post-operative hyponatraemia due to either the syndrome of inappropriate antidiuretic hormone (SIADH) or cerebral salt wasting. No other factor was independently predictive of incident seizures, including tumour type, the lobe of the brain affected, the amount of operative blood loss, and the length of surgery [179]. Consequently, though children and adolescents who are awaiting brain-tumour resection and have recurrent seizures might warrant the initiation of an AED pre-operatively, and perhaps also children under age two years with a supratentorial tumour and those with highly-epileptogenic tumours like DNETs, even in the absence of seizures, the prophylactic use of these drugs is far from empirically justified. What is more prudent is to monitor all patients carefully throughout the peri-operative period to identify clinical factors that might place the child at risk, like electrolyte imbalances and fever.

### **3.2. AEDs for seizure control**

Although in some small series of patients, seizures have been found to occur in up to 50% of paediatric patients with a brain tumour [170], in most populations, the overall incidence of seizures in this patient population is considerably lower, in the 10-20% range [51, 89, 90]. This is largely due to the infratentorial location of the majority of paediatric tumours, where very few are epileptogenic [37]. As such, only a small minority of children and adolescents with a brain tumour will likely ever require an AED, and almost all will have a supratentorial lesion. For example, from a database of 334 patients up to 21-years old, Sogawa et al. only identified 32 (10%) who had been started on an AED [83]; 94% of these 32 tumours were supratentorial, and 78% were glial [83]. Similarly, in their series of 280 patients between the ages of two months and 18 years of age, Khan et al. identified only 55 (20%) patients who had required an AED, among whom 49 (89%) had a supratentorial lesion [90]. This being said, over a 20-year period at a single institution, Khan et al. followed 157 patients who had presented with seizures and a brain tumour during childhood or

adolescence, all of whom had been on at least one AED at some point [82]. Of these patients, phenytoin was the first AED used for 52 patients, carbamazepine for 38 patients, gabapentin for 31, and phenobarbital for 14. Sixty-two of these patients ultimately were taken off all AEDs; but 17 of these 62 (27%) suffered seizure recurrence [181].

DNETs and gangliogliomas, which typically become manifest during childhood, adolescence or young adulthood, represent only a small percentage of CNS tumours in either youths or adults [6]. However, these tumours are almost always associated with seizures. Consequently, they comprise a disproportionate percentage of tumour-associated epilepsy cases [28, 44, 62, 73, 88, 89, 91, 94, 95]. Moreover, DNETs tend to be extremely resistant to AED therapy [62, 182-186]. Consequently, though AEDs generally are initiated in such patients, the majority ultimately will require surgical resection.

There is virtually no debate that AEDs are of use in treating brain tumour patients with seizures, in patients with repeated seizures awaiting surgery, in patients in whom tumour resection is infeasible, and in those whose seizures remain refractory despite surgery. However, there is concern about the risks of their long-term use, especially in patients who require on-going chemotherapy for their brain malignancy due to drug interactions and mutually-shared toxicities [81, 83, 127, 140, 151, 159, 172, 176], 187]; and significant debate regarding when and how AEDs should be discontinued post-operatively.

One of the biggest issues relating to AEDs is their potential interactions with anti-neoplastic drugs administered to control tumours and prolong survival. In a paper reviewing anti-epileptic drugs, Kargiotis et al. [109] listed 25 chemotherapeutic medications that interact with AEDs, most commonly carbamazepine, phenobarbital, phenytoin and primidone, but also valproic acid. Common interactions are the AED accelerating metabolism of the chemotherapeutic drug, and the chemotherapeutic drug reducing serum levels of the AED [109], two results that potentially accentuate each other — when AED levels fall, AED doses must be increased to achieve seizure control, which will further increase metabolism of the chemotherapeutic drug, resulting in its doses needing to be increased, and so on. Included on their list of 25 drugs were 13 drugs often selected for the treatment of brain metastases, as well as nine drugs currently used to treat glioblastomas, six drugs to treat medulloblastomas, and five to treat malignant meningiomas.

In the current paper, Table 1 lists these interactions in reverse, indicating those anti-neoplastic drugs used for CNS malignancies that have had documented interactions with each of the five AEDs listed above. What is clear from this table is that all but valproic acid interacts with almost all of the chemo-therapeutic drugs typically used for CNS cancers.

The only drug on the list published by Kargiotis et al. [109] this is not considered to interact with AEDs is temozolomide (TMZ), a less toxic and more-easily tolerated orally-administered drug that effectively crosses the blood-brain barrier [188] and is now commonly used for both high-grade [189] and low-grade [190, 191] gliomas, as well as for brain metastases [192] and melanomas, often in combination with radiation therapy. There also is evidence that TMZ itself reduces the frequency of seizures, independent of AED dose. In one study in which 39 patients receiving TMZ (mean age 46.0 years) were followed for a

mean 39 months and compared with 30 patients not on TMZ (mean age 41.5 years), patients on TMZ experienced a 59% reduction in seizure frequency versus just 13% in controls ( $p < 0.001$ ) [150]. However, for reasons that are not entirely understood, TMZ appears to be less effective in children [193]. For this reason, other anti-neoplastic drugs typically are prescribed in children and adolescents, particularly multiple-drug regimens that include carboplatin and vincristine [193-195], two drugs both documented to interact with the older, cytochrome P450-inducing anti-epileptics [109] (Table 1).

Meanwhile, evidence continues to mount documenting both the effectiveness and safety of newer-generation AEDs, like levetiracetam, oxcarbazepine and pregabalin [152, 196-204]. Though direct comparisons against the older drugs are generally lacking, theoretical advantages include the lack of any effect on cytochrome P450, and the fact that these drugs generally target specific risk factors for tumour-induced seizures [81]. Recently, in a survey of 32 paediatric brain-tumour patients requiring AEDs for seizure control, Sogawa et al. found that patients who had been started on any the newer-generation drugs (levetiracetam, oxcarbazepine and lamotrigine) were three times as likely to remain on these drugs than those started on one of the older drugs like valproic acid, phenytoin, and phenobarbital (73% vs. 28%, respectively,  $p=0.04$ ) [83]. Although the sample was small, there also was evidence of increased toxicity with the older drugs, with five versus just two adverse events resulting in drug discontinuation [83].

Of course, the treatment of brain tumours is anything but a static field. In attempts to reduce tumour progression and prolong survival, newer chemotherapeutic drugs are continuously being tested. Some, like nimotuzumab [205] and bevacizumab [206], both of them antibodies against epithelial growth factor receptors (EGFR), have been demonstrating considerable promise, and this may have implications for which AEDs are best tolerated as interactions and mutual toxicities become clearer. What is evident is that AEDs, in themselves, are usually inadequate to control seizures in most patients with epileptogenic brain tumours. And while novel treatments like stereotactic radiosurgery [154], vagus nerve stimulation [207], and ionizing radiation [208] are emerging, at this time optimal management of a child or adolescent with epilepsy caused by a brain tumour almost always necessitates resection of the lesion itself.

## **4. Surgical resection of epileptogenic brain tumours**

### **4.1. The benefits and risks of surgery**

In recent years, there has been a trend towards earlier surgical intervention in young patients with low-grade epileptogenic tumours; but is this justified? One potential justification is the risk of malignant transformation of low-grade tumours which, even though uncommon, has been described for virtually all tumour types and often is catastrophic [60, 64, 65, 67, 68, 97, 112, 131, 209-213]. A second justification pertains to improved seizure control and the decreased reliance on AEDs, with some patients potentially able to discontinue anti-epileptic medications altogether<sup>59</sup>, [61, 181, 185]. But how successful is tumour resection in terms of controlling or eliminating seizures?

Table 2 lists 26 studies [35, 51, [61-63, 86, 90, 94, 96, 132, 148, 149, 168, 182, 184, 185, 214-223] published over the past two decades in which seizure outcomes in children and adolescents undergoing surgery to remove epileptogenic brain neoplasms were examined. Across these 26 studies are 741 patients, ranging in age from one month to 21 years of age, with a mean age of 9.1 years and a mean duration of post-operative follow-up of more than four years (overall mean=52 months, with individual study means ranging from 12 to 148 months). Though one study [86] included six paediatric patients with high-grade gliomas (either GBM or grade III astrocytoma), and another indicated 11 patients with either grade III or grade IV lesions [35], almost all of the remaining 724 patients had low-grade (grade I or II) lesions, including various low-grade gliomas and glioneuronal tumours, and less typically epileptogenic tumours like craniopharyngiomas and a dysplastic cyst. Spanning these studies, surgical approaches clearly differed, with some surgeons either largely or exclusively performing lesionectomies alone, others performing further procedures like partial lobectomies [86, 148] and amygdalohypocampectomies [182], and still others using various intra-operative mapping technologies like electrocortography (ECoG) [63, 132, 184, 214] to identify and ultimately resect extra-tumoral epileptogenic tissue. However, the ubiquitous goal was total tumour resection, whenever possible, an objective that was achieved in roughly two-thirds of cases.

Overall, the series with the lowest total resection rates were those that included a number of oligodendrogliomas (ODG), with resection rates ranging from 30% in a study exclusively of ODG and ODG-mixed lesions [96] and 40% in an older study in which half the patients had ODG [219], to 58% and 61% in studies in which the proportion of ODG was considerably lower [90, 220]. This discovery is not unexpected, given the highly infiltrative nature of these tumours [77, 96, 97, 191].

The outcomes of surgery otherwise were impressive, with almost four out of every five patients (77.7%) seizure free at the time of the final follow-up assessment, and 92.6% experiencing a significant improvement in their seizures from baseline, to Engel class 1, 2 or 3. Examining these data further reveals moderately strong, borderline statistically-significant correlations between the percentage of total resections achieved within any given series and the rate of seizure freedom ( $r=0.37$ ,  $p=0.08$ ), and between the percentage of total resections and the percentage of patients whose seizures were improved post-operatively ( $r=0.36$ ,  $p=0.09$ ). However, no correlation is apparent between the duration of follow-up and either outcome ( $r=0.06$ ,  $p=0.78$  and  $r=0.26$ ,  $p=0.22$ , respectively), suggesting that it was the surgical procedure, rather than post-operative management, that influenced seizure outcomes.

There also were no peri-operative deaths among the 741 patients, some of whom even underwent second procedures to resect residual tumour detected by imaging after the first procedure. The overall operative complication rate, adjusted for missing data, was 11.7%, with the vast majority of complications and new neurological deficits transient and completely resolved within weeks to months of the procedure. As stated above, a small number of patients required repeat surgeries to achieve seizure control, sometimes associated with total tumour resection. For example, in one series a second surgery was required in three of 29 paediatric patients with supratentorial gangliogliomas, and all became seizure free after the second operation [216].

The studies by Jo et al. [223] and Gaggero et al. [35] are of special note because all the patients were infants, under the age of 5 and 3 years, respectively. In the first small series of 14 patients

of mean age 2.7 years (32 months) [223], total resection of the epileptogenic lesion was achieved in 71%, as was total seizure freedom an average of 35 months post-operatively. In addition, all 14 infants experienced a significant reduction in seizure frequency, either being totally seizure free or having seizures limited to auras alone [223]. There also were no deaths and no reported operative complications. In the second study, which included 20 infants under age 3 years (mean age 1.5 years), eleven of the 20 children had either a grade III or grade IV neoplasm, including four choroid plexus carcinomas, one anaplastic oligodendroglioma, one anaplastic ependymoma, one immature teratoma, two glioblastoma multiforme, one PNET and one neuroblastoma [35]. Despite this, total resection was achieved in 70% of the children, seizure freedom beyond four years in 55%, and seizure improvement in 90%. Interestingly, all 20 patients lived beyond four years, and 17 remained alive at eight years of follow-up [35]. These two studies that imply both the effectiveness and safety of aggressive brain tumour resection in infants is counter to another study on 18 infants under one year of age who had a variety of grade I through IV lesions [170]. In this series, there was only one peri-operative death, due to massive brain haemorrhage in an 8-month old child with a deep, right parieto-occipital ganglioglioma. However, three patients had new-onset seizures following surgery, and an additional three had worsened neurological deficits. Of the nine patients who had pre-operative seizures, three improved, five did not improve, and one died. Overall, as of the paper's publication, only eight of the twenty patients had survived beyond infancy, with five now into adulthood (ages 18 – 26) [170]; two of the adult survivors were severely disabled at the time of the report, both having a Karnofsky score [224] of just 40%.

Also worth noting from Table 2 are the six studies in which only patients with dysembryoplastic neuroepithelial tumours (DNETs) were included (Table 3) [61, 62, 94, 132, 182, 184]. These six studies encompass 132 patients, of mean age 9.7 years, amongst whom total tumour resection was achieved in almost 82%, seizure freedom in 87%, and seizure improvement in all but a single patient (99%). However, the adjusted surgical complication rate was slightly higher than that noted across all 26 studies.

Table 4 lists four additional studies of note. Among these four additional studies, three were excluded from the previous table and its summation totals because vascular and other non-neoplastic lesions were intermingled with non-vascular lesions, with no data provided to distinguish between them; and the fourth was excluded because all the patients had tuberous sclerosis, in which brain tumors often cause uncontrolled seizures [225, 226]. The fifteen patients in this fourth study all had subependymal giant cell astrocytomas (SEGA), a tumour that is found in between five and fifteen percent of TS patients [123], typically developing in the region of the foramen of Monro, where it frequently causes obstructive hydrocephalus. Seizures primarily result from a broad array of intra-cerebral tumors, which include the cortical tubers mentioned above, and subependymal nodules, in addition to SEGA [225, 226]. The long-term prognosis therefore is poor, with death primarily resulting from intractable seizures or SEGA-induced obstructive hydrocephalus [225, 226]. As such, it is not unexpected that Cuccia et al. [99] failed to achieve either seizure freedom or any meaningful clinical improvement in seizure frequency in any of their patients. The inherent complexities of SEGA removal, given the relative inaccessibility of these tumours, also could account for the high complication rate (6 of 15, 40%).

The three remaining studies [117, 227, 228] involved a high proportion of non-neoplastic lesions that were not analyzed distinctly from neoplastic cases. Mean seizure free rates across the three studies ranged from a low of 56% to a high of 81%, with seizure improvement noted in 81.3% and 92.4% in the two studies in which this outcome was reported [117, 227]. Although no deaths were reported, almost one in four patients (73 of 320, 22.8%) had a significant post-operative complication, likely due to the highly vascular nature of many of the lesions and the increased risk of intracranial bleeding.

#### 4.2. Post-operative management

According to the 30 studies (26+4) analysed above, the rate of post-operative complications among patients with epileptogenic brain tumours is low, likely somewhere between 10 and 20 percent, depending upon the nature of the tumour resected, its location, and perhaps other factors as well. The risk of peri-operative mortality also appears to be exceedingly low, with not a single surgery-related death reported among those 873 patients.

Few papers have been published on the post-operative management of paediatric brain tumour patients. What has been reported is that youths tend to experience different intra-operative and post-operative complications than adults, and that these complications affect both short and long-term outcomes, including disability, mortality and hospital and PICU lengths of stay and, hence, direct health care costs [229, 230]. Among the various risk factors for complications are fluid and electrolyte imbalances, which may be especially significant in children. One also must consider that volume of blood loss is all relative to the age and size of the child, given that a human's total blood volume varies dramatically relative to their age and size: falling from roughly 85 to 90 ml per kg in term neonates, to roughly 85 ml/kg in infants, 80 ml/kg in children under age 10, 70-75 ml in children > 10 and adolescents, and 70ml/kg in adults [231, 232]. Clearly then, 100 ml of blood loss may mean nothing to an adult, but may represent 25% or more of the total blood volume of a newborn.

In general, the most common fluid and electrolyte abnormalities observed after brain surgery in children relate to serum sodium levels, with hyponatraemia secondary to either the syndrome of inappropriate diuretic hormone (SIADH) secretion or cerebral salt wasting syndrome, and hypernatraemia caused by diabetes insipidus (DI) [233-236]. In one series of 79 children, for example, water and sodium disorders were noted in 36 (46%): 23 (29%) with DI, 12 (15%) with SIADH, and a single patient with cerebral salt wasting [236]. Why this is especially important in the paediatric patient in whom an epileptogenic brain tumour has been resected is that sodium disturbances are a significant risk factor for seizures. In one study involving 223 paediatric patients with epileptic brain tumours undergoing 229 surgical procedures, post-operative hyponatraemia — due to either SIADH or cerebral salt wasting — was one of just three independent factors associated with peri-operative seizures, the other two being a supratentorial tumour and patient age less than two years [179].

In another study of 105 paediatric patients post brain tumor resection admitted to the PICU, patients required an average of 0.7 unexpected intensive care unit interventions, mostly secondary to sodium abnormalities, followed by new neurologic deficits, paresis, and seizures

[237]. Interestingly, however, 68% of the patients were stable enough to be transferred out of the PICU within 24 hours of surgery.

With respect to anti-epileptic drugs, the same applies post-operatively as pre-operatively, in that there is generally no need to initiate AEDs in patients who have not yet experienced seizures, given the lack of evidence documenting any benefit of prophylaxis [180, 238]. This being said, there are no clear guidelines as to when and how to discontinue AEDs if they have been initiated pre-operatively, and there is always the potential risk of withdrawal-induced seizures [59]. In one study of 332 mostly adult patients, but including some as young as age 16, among those with AEDs that had been initiated to treat seizures pre-operatively, patients with a longer history of seizures ( $p < 0.001$ ) and those with simple partial seizures ( $p = 0.004$ ) were found to be especially likely to continue to have seizures in the immediate post-operative period, as well as poorer control long-term [58]. If AEDs are started post-operatively to reduce the risk of seizures following the trauma of surgery in a patient who otherwise has not had seizures, they generally should be administered short-term [239].

## 5. When seizures persist or recur

In virtually every series we have reviewed, patients were described who underwent resection of their epileptogenic brain tumour, with apparently successful removal of the tumour, yet no achieved control of seizures. Additional patients were noted to suffer from the post-operative onset of new seizures [170]. And still others had complete control of their seizures, only to relapse later, either while still on an anti-epileptic drug or after all AEDs had been withdrawn. Each of these three scenarios has implications with respect to patient prognosis and management.

### 5.1. Implications of post-operative seizures

The clinical implications of seizures that either start or re-start months or years after the initial resection of tumour are somewhat different than seizures that start immediately post-operatively or that started pre-operatively and failed to resolve with surgery. The major concern with the latter two scenarios is that tumour resection either was incomplete, or that extra-tumoral epileptogenic tissue was not removed. Over the years, attempts have been made to optimize the resection of epileptogenic lesions by both better delineating their margins and identifying extra-tumoral epileptogenic tissue, using intra-operative tools like electrocorticography (ECoG) to identify potential seizure-inducing tissue irregularities like cortical dysplasia [63, 77, 93, 132, 1<sup>63</sup>, 184, 214, 216, 240, 241]. This has led to debate regarding the relative benefits and safety of performing epilepsy surgery rather than just lesionectomies in patients with tumour-triggered seizures [242]; though, in fact, many surgeons have been utilizing additional surgical steps like lobectomies, amygdalohypocampectomies and, in extreme cases, hemispherectomies for decades [63, 86, 94, 117, 132, 148, 149, 168, 182, 185, 214, 217, 218, 222, 227, 243]. To date, almost no direct empirical comparisons have been undertaken. In perhaps the most methodologically sound study, Gelinas et al. retrospectively compared

34 patients who underwent ECoG-aided epilepsy surgery and 33 patients who had undergone simple lesionectomies without ECoG, all between the ages of 3 months and 16 years, in Vancouver, Canada [214]. One year post-operatively, the two treatment arms were virtually identical, with roughly 80% of patients in each group seizure free. However, at a mean follow-up of 5.8 years, there was a trend towards improved seizure freedom in patients in the ECoG group, with 79% versus 61% patients still seizure free ( $p=0.08$ ). The investigators also noted no increase in neurological morbidity among patients who had undergone the more extensive ECoG-guided cortical resection, and that these patients were less likely to require repeat epilepsy surgery [214]. Why this has implications post-operatively relates to the potential need for re-operation, as discussed in the next section.

If the major concern of continued seizures is residual tumour or other epileptogenic tissue, the major concerns with later tumour recurrence are multiple. They include the possibility: (1) that the tumour itself is re-growing, having never been fully resected; (2) that the tumour has undergone malignant transformation; or (3) that some secondary tumour has started to develop, perhaps as a consequence of brain irradiation, chemotherapy, or some other cause. The risk of second brain malignancies is especially high in patients with CNS tumour-associated familial syndromes like neurofibromatosis types 1 [121] and 2 [122], tuberous sclerosis [123], von Hippel Lindau disease [244, 245], and basal cell nevus syndrome [246], with some of these tumours originating within the brain and others the result of metastatic spread from some extra-cranial site. All of the above-mentioned scenarios warrant investigation, which will include diagnostic imaging, due to their potentially dire consequences

Re-growth of tumour is anticipated among children with high-grade lesions, especially glioblastomas [81, 146, 247]. However, although long-term prognoses remain dismal, small improvements in survival times are being reported even among patients with GBMs, relating to advanced surgical techniques, the introduction of real-time, intra-operative imaging and brain mapping, and combining TMZ with radiation therapy [147, 189, 247-250]. Recall that in one study in which eleven of the 20 children had either a grade III or grade IV lesion, including two GBMs, a grade IV PNET, and a grade IV neuroblastoma, all 20 patients lived beyond four years [35]. Nonetheless, when the return of seizures leads to the discovery of grade IV tumour progression, surgery is almost never indicated. Instead, radiation therapy, chemotherapy, or both can be used and may be effective at reducing seizures [81, 208]. The recurrence of seizures does not necessarily indicate tumour progression, however. Sometimes, intrinsic changes within the tumour itself render AEDs less effective, so that switching or combining drugs may be beneficial [72]. As mentioned in Section 3, in such cases, care must be taken to avoid interactions between chemotherapeutic and anti-epileptic drugs [109].

Tumour re-growth also in anticipated in many low-grade gliomas and other neuroglial tumours when total resection is not achieved, and this can be manifested by the recurrence or worsening of seizures. This being said, malignant transformation has been documented with virtually every form of low-grade brain tumour, especially low-grade gliomas [65, 68, 112, 131], but also traditionally-benign lesions like DNETS [64, 67, 209-211], gangliogliomas [209, 212], meningiomas [251, 252], vestibular schwannomas [251], pituitary adenomas [251], and haemangioblastomas [251], among others. Glioblastomas have even been documented to arise

at the site of previously totally-resected tumours [253]. Previously-controlled seizures generally are harder to control once malignant-transformation has occurred, even independent of tumour size or rate of progression [78]. Identification of such transformation therefore has implications in terms of patient prognosis, and management of both the tumour and the seizures.

Finally, the late recurrence of seizures can represent the formation of a secondary tumour, perhaps induced by brain irradiation or chemotherapy [251].

## 5.2. Surgical management of persistent and recurrent seizures

Whether seizures start immediately after surgery, later along in follow-up, or never fully remit, in all three scenarios, some patients will have seizures that remain uncontrolled despite the use of AEDs. In our review of the 26 studies listed in Table 2, as well as in various other case series and case studies, we found that, occasionally, patients undergo second or even third resections to remove either residual tumour that is now identified on post-operative imaging, or a residual or newly-identified epileptogenic focus. Though sometimes prolonged attempts are made to control the seizures with medication prior to the second surgery, in some cases, surgery is almost immediate, even within a few days of the initial procedure [254]. In one multi-centre survey that involved 116 children under age 3 undergoing epilepsy surgery for a variety of causes, 27 children were brought into the operating room for a second procedure, and six of these for a third procedure to control seizures [171]. Both the approaches and results of these second operations are mixed. In terms of the former, attempts are usually made to resect any residual or newly-discovered tumour, as well as to identify and resect other epileptogenic foci. Approaches range from simple lesionectomies to lobectomies and, in the most severe cases, hemispherectomies [243].

Table 5 summarizes ten studies we identified, published over the past two decades, in which second operative procedures were performed [46, 77, 157, <sup>1</sup> [6]<sup>2</sup>, 171, 216, 242, 254-256]. Half of these studies were exclusive to paediatric patients, while the other half included children, adolescents and adults. The study by Steinbok et al. was restricted to infants under the age of 3 years at the time of their initial surgery [171]. In this study, six of the patients required a third surgical procedure prior to achieving their final seizure outcome. Follow-up for most of these studies was approximately two years, but sometimes not reported. Overall, slightly less than half of the patients (46%) achieved seizure freedom, with roughly half the remainder (where reported) achieving at least a significant reduction in seizures. As with the first procedures, operative mortality was low, with only one death in 132 patients and 138 procedures.

## 6. Conclusions

A brain tumour is identified in one to three percent of non-febrile seizures that occur in a child. Meanwhile, seizures occur in between one in ten and one in five paediatric patients with a brain tumour, often as a presenting symptom. Most are associated with low-grade gliomas, like pilocytic astrocytoma, or with neuroglial tumours like ganglioglioma or dysembryoplastic

neuroectodermal tumour (DNET). There is no empirical justification for initiating an anti-epileptic drug in a brain tumour patient without seizures, and some would restrict their use to those patients who experience at least two ictal episodes.

The cornerstone of management in most patients with a low-grade lesion is surgical resection, both because doing so often prolongs survival and reduces or eliminates seizures. Overall, almost 80% of children who undergo surgery to for resection of an epileptogenic brain tumour will attain prolonged seizure-freedom, and more than 90% will experience at least some meaningful clinical improvement, associated with a negligible risk of death in experienced surgical hands. Risks may be greater and results poorer in very small infants (under one year of age), but most-preschool children can undergo epilepsy-lesion resections safely and with benefit. Significant surgical complications occur in 10-20% of patients and include fluid and electrolyte imbalances, as well as typically short-lived neurological deficits in most patients, so that vigilant post-operative monitoring is essential.

Late post-operative seizure recurrence is an ominous sign that can be a harbinger of tumour recurrence, progression, or malignant transformation, as well as the appearance of new tumours, especially in patients with familial tumour syndromes like neurofibromatosis and tuberous sclerosis, and those who have received brain irradiation. When low-grade tumours recur and cause seizures, second resections may be effective at again controlling seizures.

These claims must be interpreted with caution, however, given that many essential questions remain unanswered — like whether more extensive epilepsy surgery is more effective or as safe as lesionectomy alone; and what factors best predict outcomes. In addition, with the emergence of new anti-epileptics, new anti-neoplastic treatments, and new surgical technologies, the management of epilepsy in children and adolescents with brain tumours appears to be rapidly changing.

AED	Interactions with
Phenytoin	carboplatin, cisplatin, cyclophosphamide, dacarbazine, erlotinib, etoposide, fluorouracil, ifosfamide, imatinib, irinotecan, carmustine, lomustine, paclitaxel, procarbazine, tegafur, teniposide, thiotepa, topotecan, vincristine
Carbamazepine	cisplatin, cyclophosphamide, erlotinib, etoposide, ifosfamide, imatinib, irinotecan, carmustine, lomustine, paclitaxel, procarbazine*, teniposide, thiotepa, topotecan, vincristine
Phenobarbitol	cyclophosphamide, erlotinib, etoposide, ifosfamide, imatinib, irinotecan, carmustine, lomustine, paclitaxel, procarbazine, teniposide, thiotepa, topotecan, vincristine
Primidone	cyclophosphamide, erlotinib, etoposide, ifosfamide, imatinib, irinotecan, carmustine, lomustine, paclitaxel, procarbazine, teniposide, thiotepa, topotecan, vincristine
Valproic Acid	cisplatin, cyclophosphamide, vorinostat

\*Carbamazepine is contraindicated in patients on procarbazine

**Table 1.** Anti-epileptic drugs (AED) and their interactions with CNS anti-neoplastic drugs

First Author	Year Published	# Subjects	Mean Age (y)	Age Range	Tumour Types	Surgical Procedure	# Total Resection	% Total Resection	Mean FU (mo)	# Seizure Free	% Seizure Free	# Improved	% Improved	# Peri-Op Deaths	# Surgical Compl.
Ramantani	2014	29	11.7	2y - 17y	GG, DNET	L+E	16	55.2%	148	22	75.9%	29	100.0%	0	2
Consales	2013	22	6.5	10m - 16y	GG, DNET	L	15	68.2%	12	20	90.9%	22	100.0%	0	0
Babini	2013	30	12.1	3y - 18y	GG, DNET, PGNT	L, L+E	30	100.0%	85	26	86.7%	30	100.0%	0	1
Fattal-Valevski*	2013	54	7.1	1m - 19y	LGG, DNET	?	?	?	24	38	77.6%	51	94.4%	0	4
Jo	2013	9	2.7	6m - 5y	GG(2), AC(2), ODG, DNT, PNET, CPP, CP	L	7	77.8%	63	7	77.8%	9	100.0%	0	0
Uluel-Sibony	2011	41	8.2	1y - 18y	LGG, DNET	L, L+A	35	85.4%	62	34	82.9%	36	87.8%	0	2
Gelinas	2011	67	9.1	3m - 16y	43 LGG, 11 DNET, 14 other	L vs. L+ECoG	65	97.0%	12	52	77.6%	?	?	0	13
Spalice	2010	13	6.7	1y - 14y	DNET	L+E	12	92.3%	78	13	100.0%	13	100.0%	0	1
Ogiwara	2010	30	8.6	9m - 16y	GG	L, L+E	29	96.7%	62	27	90.0%	30	100.0%	0	2
Bilginer	2009	29	10.7	3y - 21y	DNET	TL±AHC	?	?	52	27	93.1%	29	100.0%	0	?
Lee	2009	22	12.4	3y - 18y	DNET	L±L	22	100.0%	44	20	90.9%	22	100.0%	0	1
Gaggero	2009	20	1.5	1m - 3y	Grade II(5), III(4), IIII(7), IV(4)	L	14	70.0%	48	11	55.0%	18	90.0%	0	?
Minkin	2008	24	8.9	1y - 15y	DNET	L	21	87.5%	80	20	83.3%	24	100.0%	0	9
Kan***	2008	16	?	2y - 21y	GG, DNET, LGG	L+E	?	?	(1 - 8 y)	13	81.3%	15	93.8%	0	?
Khan	2006	55	9.3	2m - 18y	LGG, DNET, ODG	L	32	58.2%	54	46	83.6%	50	90.9%	0	?
Cataltepe	2005	29	10.5	2y - 18y	GG, DNET, AC (T)	L, L+L+A, L+L	18	62.1%	31	20	69.0%	24	82.8%	0	5
Sandberg	2005	18	9.6	1m - 13y	DNET	L±mapping	18	100.0%	19	18	100.0%	18	100.0%	0	1
Giulioni	2005	15	12.6	3y - 18y	GG, DNET	L	13	86.7%	67	13	86.7%	15	100.0%	0	2
Nolan	2004	26	10.0	4y - 18y	DNET	?	11	42.3%	52	16	61.5%	25	96.2%	0	?
Im**	2002	18	9.2	1y - 16y	GG	L	14	77.8%	48	15	83.3%	18	100.0%	0	?
Kim	2001	23	7.9	8m - 15y	DNET, ODG, GG	L, L+E	14	60.9%	43	16	69.6%	21	91.3%	0	7
Ianelli*	2000	37	9.1	1y - 15y	LGG (31), HGG (6)	L, L+L+A, L+L	22	59.5%	72	26	81.3%	37	100.0%	0	3
Khajavi	1999	34	12.6	1.5y - 18y	GG, LGG, DNET	L, lobectomy	28	82.4%	43	25	73.5%	29	85.3%	0	5
Razach	1998	10	11.2	1y - 16y	ODG/mixed ODG/AC	L	3	30.0%	40	?	?	3	30.0%	0	?
Kim	1995	10	9.8	1y - 15y	5 ODG, 3 LGG, PNET, vasc	L	4	40.0%	40	6	60.0%	9	90.0%	0	?
Packer	1994	60	10.6	1y - 20y	LGG, GG	L, L+E	47	78.3%	24	45	75.0%	47	78.3%	0	?
<b>TOTALS</b>		<b>741</b>	<b>9.1</b>	<b>1m - 19y</b>			<b>490</b>	<b>66.1%</b>	<b>51.9</b>	<b>576</b>	<b>77.7%</b>	<b>624</b>	<b>92.6%</b>	<b>0</b>	<b>58</b>
														<b>0.0%</b>	<b>7.8%</b>
															<b>Adjusted = 11.7%</b>

\* some patients died before final seizure assessment; \*\* three patients underwent a second resection; \*\*\* these 16 patients part of a larger series with other seizure aetiologies included  
 GG = ganglioglioma; DNET = dysembryoplastic neuroepithelial tumor; PGNT = papillary glioneuronal tumor; LGG = low-grade glioma; ODG = oligodendroglioma; AC = astrocytoma; CPP = choroid plexus papilloma; CP = craniopharyngioma  
 L = lesionectomy; L+E = lesionectomy + additional resection of adjacent epileptogenic tissue; L+A = lesionectomy + amygdalohypocampectomy; L+L = lesionectomy + lobectomy;  
 TL = temporal lobectomy; L+L+A = lesionectomy + lobectomy + amygdalohypocampectomy; AHC = amygdalohypocampectomy; (T) = all temporal lesions  
 ? = missing data

\* Some patients died before final seizure assessment; \*\* Three patients underwent a second reaction; \*\*\* These 16 patients part of a larger series with other seizure aetiologies included

GG=ganglioglioma; DNET=dysembryoplastic neuroepithelial tumor; PGNT=papillary glioneuronal tumor; LGG=low-grade glioma; ODG=oligodendroglioma; AC=astrocytoma; CPP=choroid plexus papilloma; CP=craniopharyngioma; L=lesionectomy; L+E=lesionectomy+additional resection of adjacent epileptogenic tissue; L+A=lesionectomy+amygdalohypocampectomy; L+L=lesionectomy+lobectomy; TL=temporal lobectomy; L+L+A=lesionectomy+lobectomy+amygdalohypocampectomy; AHC=amygdalohypocampectomy; (T)=all temporal lesions

**Table 2.** Seizure response to surgical resection of epileptogenic tumor

First Author	Year Published	# Subjects	Mean Age (y)	Age Range	Tumour Types	Surgical Procedure	# Total Resection	% Total Resection	Mean FU (mo)	# Seizure Free	% Seizure Free	# Improved	% Improved	# Peri-Op Deaths	# Surgical Compl.
Spalice	2010	13	6.7	1y - 14y	DNET	L+E	12	92.3%	78	13	100.0%	13	100.0%	0	1
Bilginer	2009	29	10.7	3y - 21y	DNET	TL±AHC	?	?	52	27	93.1%	29	100.0%	0	?
Lee	2009	22	12.4	3y - 18y	DNET	L±L	22	100.0%	44	20	90.9%	22	100.0%	0	1
Minkin	2008	24	8.9	1y - 15y	DNET	L	21	87.5%	80	20	83.3%	24	100.0%	0	9
Sandberg	2005	18	9.6	1m - 13y	DNET	L±mapping	18	100.0%	19	18	100.0%	18	100.0%	0	1
Nolan	2004	26	10.0	4y - 18y	DNET	?	11	42.3%	52	16	61.5%	25	96.2%	0	?
		<b>132</b>	<b>9.7</b>				<b>84</b>	<b>81.6%</b>	<b>54.2</b>	<b>114</b>	<b>86.4%</b>	<b>131</b>	<b>99.2%</b>	<b>0</b>	<b>12</b>
															<b>15.6%</b>

**Table 3.** Seizure response to surgical resection of dysembryoplastic neuroectodermal tumors

First Author	Year Published	# Subjects	Mean Age (y)	Age Range	Tumour Types	Surgical Procedure	# Total Resection	% Total Resection	Mean FU (mo)	# Seizure Free	% Seizure Free	# Improved	% Improved	# Peri-Op Deaths	# Surgical Compl.
Kim	2008	134	8.5	8m - 18y	various, incl. vasc.	various	?	?	62	93	69.4%	109	81.3%	0	23
Cuccia	2003	15	10.5	4.5y - 19y	SEGA (+TS)	L	12	80.0%	52	0	0.0%	0	0.0%	0	6
Sonderkaer	2003	18	?	?	various	?	?	#VALUE!	128	10	55.6%	?	?	?	?
Borgeois	1999	171	8.3	10m - 15y	~40 vascular, etc	various	?	?	62	139	81.3%	158	92.4%	0	44

vasc. = vascular lesion; SEGA = subependymal giant cell astrocytoma; TS = tuberous sclerosis; FU = follow-up

Vasc=vascular lesions; SEGA=subependymal cell astrocytoma; TS=tuberous sclerosis; FU=follow-up

**Table 4.** Seizure response to surgical resection of epileptogenic tumor – studies including vascular lesions

First	Year	#	Mean	#
Author	Published	Subjects	Age (y)*	Seizure Free
Benifla	2006	12	13.5	7
Chae	2001	1	0.3	1
Gonzalez-Martinez	2007	57	24.7	22
Im	2002	3	16.5	3
Jooma	1995	8	24.0	5
Lombardi	1997	1	?	1
Ojemann	2012	4	8.5	2
Steinbok	2009	24	1.5	12
Tian	2011	9	13.7	3
Whittle	1995	4	36.0	0
Totals		123		56
Mean			15.4	
Percentages				45.5%

**Table 5.** Seizure response to a second surgical resection

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