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Rates and predictors of seizure freedom in resective epilepsy surgery: an update

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Abstract

Epilepsy is a debilitating neurological disorder affecting approximately 1 % of the world's population. Drug-resistant focal epilepsies are potentially surgically remediable. Although epilepsy surgery is dramatically underutilized among medically refractory patients, there is an expanding collection of evidence supporting its efficacy which may soon compel a paradigm shift. Of note is that a recent randomized controlled trial demonstrated that early resection leads to considerably better seizure outcomes than continued medical therapy in patients with pharmaco-resistant temporal lobe epilepsy. In the present review, we provide a timely update of seizure freedom rates and predictors in resective epilepsy surgery, organized by the distinct pathological entities most commonly observed. Class I evidence, meta-analyses, and individual observational case series are considered, including the experiences of both our institution and others. Overall, resective epilepsy surgery leads to seizure freedom in approximately two thirds of patients with intractable temporal lobe epilepsy and about one half of individuals with focal neocortical epilepsy, although only the former observation is supported by class I evidence. Two common modifiable predictors of postoperative seizure freedom are early operative intervention and, in the case of a discrete lesion, gross total resection. Evidence-based practice guidelines recommend that epilepsy patients who continue to have seizures after trialing two or more medication regimens should be referred to a comprehensive epilepsy center for multidisciplinary evaluation, including surgical consideration.

Keywords

Epilepsy surgery; Resection; Review; Seizure outcome

Introduction

Epilepsy is a debilitating neurological disorder affecting approximately 1 % of the world's population, producing a tremendous societal burden [9, 49]. Though common, drug-resistant focal epilepsies are potentially surgically remediable. Perspectives related to epilepsy surgery have progressed considerably over the past several decades, as recently summarized by Wilson and Engel [210], with a few notable developments in just the past year. With

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regard to palliative non-resective epilepsy surgery, the past 1–2 years have seen the approval of NeuroPace—a new implantable neurostimulation device for epilepsy [82]—as well as the 100,000th implantation of a vagus nerve stimulator [44]. More importantly, however, Engel and colleagues [61] recently reported the much anticipated results of a randomized controlled trial investigating the clinical effectiveness of early resective epilepsy surgery in patients with temporal lobe epilepsy (TLE) [61]. Only the second randomized controlled trial to address resective epilepsy surgery, this study demonstrated convincingly that early surgical intervention in patients with newly refractory TLE produces better seizure outcomes than continued conservative drug therapy. Some have speculated whether this pivotal trial might facilitate a paradigm shift in the treatment of focal epilepsy [120, 174]. Specifically, whereas many practitioners have thus far been hesitant to consider invasive surgery for pharmacoresistant patients—instead pursuing years to decades of new medication combinations with marginal success—these novel data may influence earlier referral for surgical consideration [62, 102, 127].

There is also reason to be skeptical that the findings of Engel and colleagues will stimulate any meaningful paradigm shift. After the first randomized controlled trial by Wiebe et al. in 2001 [207] revealed dramatically improved seizure outcomes with epilepsy surgery over medical therapy in refractory TLE patients [207], consensus guidelines recommended early surgical referral of pharmacoresistant epilepsy patients [41, 62, 63, 128]. At that time, there was anticipation of an increase in surgical referrals [59], but large epilepsy centers did not experience the expected increase in patient volume [60, 102]. In fact, two studies in the past year examining US hospital data from the Nationwide Inpatient Sample—reported independently by our group and by Schiltz et al.—revealed no change in the utilization of epilepsy surgery during the 2000s, despite class I evidence and clear practice parameters [73, 173]. Furthermore, it was found that epilepsy patients are increasingly being treated at low-volume community hospitals, rather than high-volume epilepsy centers, and that these smaller institutions are less likely to perform surgery [74]. It remains unclear whether new class I data supporting epilepsy surgery will significantly influence its persistent underutilization. Nevertheless, the recent refocus on the issue allows a timely opportunity for an inclusive update on seizure outcomes after epilepsy surgery, considering temporal lobectomy and other resective procedures.

In the present review, our goal is a concise but thorough summary of seizure freedom rates and predictors in the surgical treatment of epilepsy, with particular focus on class I evidence and our own institutional experiences. “Seizure freedom” will be defined as a lack of disabling seizures, or a class I seizure outcome using the grading scale by Engel and colleagues [57], and predictors of seizure freedom will refer to modifiable and fixed variables significantly associated with an Engel class I outcome. Both children and adults will be considered. Palliative non-resective epilepsy surgery, including disconnection procedures and neurostimulation device implantation, will not be discussed.

While most discussions of resective epilepsy surgery are organized by the lobe(s) harboring the epileptogenic zone, there are also important treatment nuances across the various neuropathological entities which cause focal epilepsy. Blumcke’s recent analysis of 4,512 specimens excised during resective epilepsy surgeries—the largest study of its kind—allows

insight into the commonality of these various pathological entities [18]. As reproduced in Table 1, mesial temporal sclerosis (MTS) was the most common clinicopathological finding observed (40 %), followed by brain tumors (27 %), malformations of cortical development (MCD, 13 %), and vascular malformations (6 %). Henceforth in this review, we will consider focal epilepsy etiologies in this same order.

Mesial temporal sclerosis and temporal lobe epilepsy

TLE is the most common epileptic disorder, first described in detail by Hughlings-Jackson in the late nineteenth century [65, 111]. Hughlings-Jackson suspected a mesial temporal origin of the “uncinate fit” and its resultant “dreamy state,” a phenomenon now recognized as the characteristic complex partial seizure of TLE, and its effects on higher-order association cortex involved in consciousness [68, 78, 109, 111]. While a wide variety of lesions in the mesial or lateral temporal lobe can lead to mesial or lateral TLE, respectively, the most common pathology underlying intractable TLE is MTS [18, 182]. MTS is characterized by neuronal loss, cellular reorganization, and glial proliferation in the hippocampus and may also be associated with sclerosis of the amygdala and parahippocampal gyrus [189]. It has been proposed that these and other changes lead to hyperexcitability of dentate granule cells, which spread out of the hippocampus to generate seizures [46]. Potential risk factors for developing TLE have been described and may include febrile seizures, head trauma, central nervous system infection, family history of epilepsy, alcohol or drug abuse, status epilepticus, birth injury, cerebral ischemia, and other temporal lobe lesions [84, 87].

In TLE, seizures are refractory to antiepileptic drugs (AEDs) in approximately 30 % of patients, leading to cognitive deficits, reduced quality of life, and increased risk of death [34, 60, 105]. Selecting appropriate candidates for temporal lobe resection requires comprehensive neuroimaging, electrophysiological, and neurocognitive evaluation by a team of neurologists, neuropsychologists, neurosurgeons, and neuro-radiologists. High-resolution structural magnetic resonance imaging (MRI) to evaluate for MTS or other lesions is routine, and functional neuroimaging may include positron emission tomography (PET) to search for focal hypometabolism and functional MRI or magnetoencephalography to localize language and, in some cases, interictal spikes [16, 31, 112]. At several centers, functional neuroimaging is replacing invasive WADA testing for language lateralization, but WADA remains the gold standard for memory lateralization [1, 16]. Interictal scalp electroencephalography (EEG) is often followed by longer periods of inpatient video EEG monitoring, and invasive intracranial EEG with grid, depth, and strip electrodes is used when localization of the epileptogenic zone remains in question and/or greater spatial detail is required [91, 220]. In some instances, intraoperative electrocorticography (ECoG) can be used to supplement or replace long-term intracranial EEG, particularly in patients undergoing awake speech mapping, although capturing ictal events requires implanted electrodes [11, 161]. Notably, the evaluation of extratemporal epilepsy absent a pre-localized lesion often incorporates a similar diagnostic strategy [165].

The standard of care in treating drug-resistant TLE from MTS is resective surgery with anterior temporal lobectomy (ATL) [58, 97, 182]. In both adults and children, seizure

freedom is more common after resection for MTS (60–90 %) than localized neocortical epilepsies (40–70 %), the most common being frontal lobe epilepsy [69, 75, 77]. In our own surgical series including the past 15 years, approximately 70–80 % of adults and children with TLE have achieved seizure freedom after ATL [72, 76]. Furthermore, resective TLE surgery has been validated by class I evidence through two randomized controlled trials. In the first of these trials, Wiebe and colleagues [207] found that 40 drug-resistant TLE patients who underwent ATL were significantly more likely to be seizure-free at 1 year (58 %) than 40 patients randomized to continued best drug therapy (8 % seizure-free) [207]. In a meta-analysis including this trial and 31 other studies (2,250 patients), Engel et al. [63] reported that 65 % of TLE patients achieved seizure freedom after ATL, with another 21 % experiencing an improved seizure profile [63]. Together, these results led to a joint recommendation of the American Academy of Neurology, the American Epilepsy Society, and the American Association of Neurological Surgeons that patients with medically refractory epilepsy be referred to a comprehensive epilepsy center with surgical capabilities [63].

Recently, in a second randomized controlled trial comparing ATL to continued AED therapy, Engel and colleagues [61] specifically investigated the value of early surgical intervention [61]. They found that while 73 % of 15 surgically treated individuals were seizure-free at 2 years, none of the 23 patients assigned to medical therapy reached this outcome. Furthermore, improvements in quality of life were significantly greater in the surgical group than the medical group. Overall, the data in favor of surgical resection for appropriate candidates with intractable TLE—including two randomized controlled trials and numerous observations studies—are convincing and suggest that a surgical “cure” is possible in some patients with this devastating disorder.

With regard to operative approach for mesial temporal lobe resection, most studies have shown comparable seizure outcomes between standard ATL and selective amygdalohippocampectomy (AH) [175, 215], although the latter may carry the risk of seizure recurrence in patients with an unrecognized lateral temporal epileptogenic zone [153]. While many groups have described improved memory outcomes and neuropsychological scores with selective AH over ATL [35, 142], others have reported no differences [24, 96, 212]. Finally, with careful operative technique, some authors have proposed that visual field deficits may be less pronounced with selective AH over standard ATL [136, 192].

Brain tumors

A brain tumor is the second most common cause of focal epilepsy. Tumor-related epilepsy may lead to diminished quality of life, cognitive deterioration, and significant morbidity [169, 179, 187, 221]. While the molecular mechanisms of epileptogenicity in brain tumors remain incompletely understood, pathophysiological contributions include cerebral hypoxia, neurotransmitter alterations, and disruption of the blood–brain barrier [64, 100, 119, 169, 178]. While seizures can be caused by intrinsic intra-axial tumors, metastatic tumors, or extra-axial tumors (such as meningioma), glioneuronal tumors and gliomas are the most common pathologies associated with tumoral epilepsy, and will be the subject of our focus.

Glioneuronal tumors

Unlike patients with malignant brain tumors, patients with low-grade tumors often survive many years [155, 156], making seizure freedom a critical factor in optimizing patient quality of life. Among low-grade brain tumors, glioneuronal tumors such as gangliogliomas and dysembryoplastic neuroepithelial tumors (DNETs) are most likely to present with seizures [27, 94, 141, 147]. Approximately three quarters of ganglioglioma patients present with seizures, three quarters of those have a temporal lobe lesion, and nearly half of patients with ganglioglioma progress to drug-resistant epilepsy [4, 131, 181]. With DNET, approximately half of epilepsy patients harboring this lesion also have associated cortical dysplasia [27].

Previous studies have examined seizure outcomes in the resection of glioneuronal tumors causing epilepsy, reporting postoperative seizure freedom rates of between 45 and 100 % [4, 27, 92–94, 152, 214]. In a recent retrospective series of 66 patients with ganglioglioma treated at our center, 49 of which presented with epilepsy, we evaluated long-term seizure outcomes after excision [181]. Five years after resection, 85 % of patients with a seizure history were free of seizures, including 96 % of individuals in whom gross total lesionectomy was achieved, but only 54 % of those with subtotal resection. Tumor progression occurred in 38 % of cases involving gross total resection, but in only 8 % of those associated with subtotal resection. We also evaluated 50 patients with DNET-related epilepsy surgically treated at our institution, 87 % of whom reached an Engel class I outcome after surgery [27]. Seizure freedom was again predicted by gross total resection, achieved in approximately 80 % of surgeries, and this outcome remained resilient at a median follow-up of >5 years [27]. The positive predictive value of extent of resection in glioneuronal tumor-related epilepsy surgery was also confirmed by a systematic review of 39 studies including 910 patients [67]. In this report, seizure freedom was >30 % more likely with gross total resection compared to subtotal excision and was also predicted by an absence of generalized seizures and early surgical therapy. Overall, these findings suggest that both seizure and oncologic outcomes can be excellent in glioneuronal tumor surgery, particularly with complete resection and early operative intervention.

Gliomas

World Health Organization grade II gliomas—including astrocytoma, oligodendroglioma, and oligoastrocytoma—are invasive lesions that often progress over time despite therapy [12, 28]. Seizure generation in gliomas may result in part from invasion of tumor cells into surrounding brain parenchyma as well as increased expression of fast-activating sodium channels and diminished potassium buffering within glial cells at the epileptogenic foci [20, 166]. While the oncological prognosis of gliomas is poorer than glioneuronal tumors, low-grade glioma patients may nonetheless survive >10 years with aggressive management, and seizure control is a known factor in maximizing quality of life [53, 121, 186, 195].

20, 166, 53, 121, 186, 195 Seizures are a common presenting symptom in patients with low-grade glioma, affecting 60–80 % of individuals with these lesions [158, 160, 219]. In an analysis of 332 low-grade glioma patients undergoing resection at our center, 80 % presented with seizures, and pharmacoresistance was present in half of these [32]. Seizure freedom was seen in 67 % of individuals with tumoral epilepsy after surgery, with rare

seizures observed in another 17 %, and favorable outcomes were predicted by greater extent of resection. Lesion recurrence was associated with epilepsy recurrence, further demonstrating the association between tumor burden and seizures [32]. A recent systematic review of the literature examined 773 patients with low-grade gliomas and epilepsy across 20 surgical series [66]. It was noted that about 70 % of individuals with low-grade glioma-related epilepsy become seizure-free after surgery, with predictors of this outcome including resection extent (defined as removal of tissue displaying abnormal T2 signal on postoperative compared to preoperative MRI), a shorter history of epilepsy, and preoperative seizure control on AEDs. Thus, as with glioneuronal tumors, improved seizure outcomes in low-grade glioma surgery are seen with early intervention and gross total resection, and a direct relationship between tumor burden and seizure status is likely.

High-grade gliomas are associated with a much poorer prognosis than low-grade lesions, with median survival of approximately 22 months for anaplastic astrocytoma and 12 months for glioblastoma, even with surgery, radiation, and chemotherapy [23, 42, 47, 67]. Seizures affect between 25 and 60 % of individuals with high-grade gliomas and negatively impact quality of life [26, 95, 106, 139, 154]. To our knowledge, there has only been one study investigating seizure status as a primary outcome in high-grade glioma surgery. In this retrospective case series, 1 year after surgical resection of glioblastoma in 153 patients with epilepsy, 77 % of individuals were seizure-free on medication [26]. A favorable postoperative seizure outcome was predicted by preoperative seizure control. Nevertheless, given the poor oncological prognosis associated with high-grade gliomas, the primary goal of resection remains aggressive tumor control, with surgical treatment of seizures representing a worthwhile secondary consideration [67].

Additional considerations with temporal lobe tumors

While any supratentorial tumor can cause epilepsy, patients with temporal lobe lesions are particularly prone to seizures, like due to the epileptogenicity of mesial temporal structures [32, 88, 203]. It is known that seizure freedom in tumor surgery is more common with gross total resection than subtotal lesionectomy, but an additional consideration in tumoral TLE is that dual pathology may drive ictogenesis [84, 182]. Thus, cortical dysgenesis, gliosis, and hippocampal sclerosis may permit continued seizures even after gross total excision of the primary lesion [84, 88, 203]. Some investigators have therefore argued for more extensive resection in tumor-related TLE cases, suggesting that the inclusion of hippocampectomy and anterior temporal corticectomy produces better postoperative seizure control than gross total lesionectomy alone [14, 94, 117, 148]. In such cases, perilesional parenchymal resection is often customized by interictal spike mapping via intra-operative ECoG recordings [12, 181]. In one study, Giulioni and colleagues [94] retrospectively analyzed seizure outcomes in 28 patients who received tailored surgery for temporal lobe glioneuronal tumors causing epilepsy⁹⁴. One half of the patients underwent lesionectomy alone, while the other half received lesionectomy along with customized amygdalohippocampectomy and anterior temporal corticectomy. Seizure outcomes were dramatically better in individuals who received extended resection (93 % Engel I) compared to lesionectomy alone (43 % Engel I), but other differences between patients in either group may have confounded this finding. We recently meta-analyzed extent of resection in low-grade temporal lobe tumor resections

across 41 studies including 1,181 patients [70]. Subtotal lesionectomy alone produced a postoperative seizure freedom rate of only 43 %, versus 79 % with gross total lesionectomy alone, versus 87 % with lesionectomy plus hippocampectomy and/or anterior temporal corticectomy [70]. The small but significant benefit of extended resection over gross total lesionectomy alone appears more prominent with mesial rather than lateral temporal lesion location. It is therefore possible that a larger tailored resection may be associated with better seizure outcomes in temporal lobe tumoral epilepsy surgery, but consensus recommendation would likely require controlled prospective data.

Malformations of cortical development

MCD represent a spectrum of congenital structural abnormalities of cerebral cortical growth and development. MCD range in severity from focal cortical dysplasia (FCD) to polymicrogyria and are a major cause of pharmacoresistant epilepsy [33, 151, 199]. MCD subtypes can result from abnormal (1) neuronal and glial proliferation or differentiation, (2) neuronal migration, or (3) cortical organization [130]. MCD resulting from aberrant cellular proliferation or differentiation are the most common, and under the most recent classification scheme, these include FCD, tuberous sclerosis, and hemimegalencephaly [3, 7, 130]. Epilepsy is also seen in MCD involving neuronal migration problems (lissencephaly, subcortical band heterotopia, periventricular nodular heterotopia) and abnormal cortical organization (polymicrogyria, schizencephaly), but these disorders will not be discussed here further given their relative rarity.

Focal cortical dysplasia

FCD can be defined using a three-tier system recently updated by the International League Against Epilepsy (ILAE) Task Force [19], as summarized in Table 2 [19]. Seizures are the most common presentation of FCD, and approximately one half of all epilepsy patients have some form of FCD [17]. The mechanisms of ictogenesis in FCD have been investigated in humans and animal models. These include increased excitation in dysplastic neurons produced by elevated glutamate receptor expression [38, 48, 108] as well as diminished neuronal expression of γ -aminobutyric acid (GABA) receptors within FCD lesions [83, 183].

Resection for FCD-related epilepsy can be challenging as subtle radiographic anomalies can produce devastating epileptic syndromes [36]. Rates of seizure control reported in the literature range widely from 32 to 89 % after resection [33, 103]. In a recent surgical series of 143 patients with FCD and intractable epilepsy at our institution, postoperative seizure freedom rates were 72 % at 2 years, 65 % at 5 years, and 67 % at 10 years [33]. The main predictor of seizure outcome was gross total resection delineated by both MRI and invasive ECoG recordings [33]. Other positive prognosticators included small lesion size and a focal gray-white blurring on MRI known as the transmante sign [198]. In a meta-analysis combining these results with 36 other surgical FCD series, postoperative seizure freedom was achieved by 58 % of 2,014 patients [168]. Favorable outcome was predicted by temporal lobe surgical location, abnormal MRI, type II ILAE histological classification, and complete resection of the anatomical or electrographic abnormality. Given the inherent

challenge of accurately delineating the ictogenic zone in FCD, these findings highlight the importance of high-resolution neuroimaging, meticulous electrophysiological techniques, and histopathologically proven margins in guiding the surgical excision of dysplastic lesions.

Tuberous sclerosis

Tuberous sclerosis complex is an autosomal dominant disorder resulting from mutations in the gene TSC1 (encoding hamartin) or TSC2 (encoding tuberin), leading to the formation of hamartomas and other neoplasms in multiple organ systems [40, 133]. This condition was first described in detail by Bourneville in 1880 and has an overall prevalence of approximately 1 person per 6,000 [21, 40]. Seizures are the manifesting symptom in 90 % of patients with tuberous sclerosis, often beginning in the first year of life [80]. The pathogenesis of epilepsy is incompletely understood, but has been suggested to involve abnormal GABA receptor expression and impaired glutamate transport in astrocytes [80, 204, 213].

Seizures become refractory to AEDs in the majority of children with tuberous sclerosis by 2 years of age, leading to marked cognitive impairment and developmental retardation [43, 80, 99, 113]. Therefore, early surgical intervention is often considered for patients with severe pharmacoresistant epilepsy [80]. However, bilateral or multiple epileptogenic foci are more common in tuberous sclerosis than other lesional epileptic disorders, perhaps given the frequent multiplicity of parenchymal tubers [25, 164, 202]. Therefore, the appropriate selection of surgical candidates requires meticulous preoperative evaluation with high-resolution neuroimaging and electrophysiologic recordings and often includes invasive intracranial recordings [25, 80].

Seizure outcome data for tuberous sclerosis surgery are somewhat limited as most published patient cohorts are small and retrospective. However, two independent systematic reviews have helped to summarize relevant cases throughout the literature. Jansen et al. [114] examined 25 articles including 177 epilepsy patients receiving resective surgery for tuberous sclerosis. After post-surgical follow-up of 1 year, patients experienced a 90 % decrease in seizure frequency, with 57 % of individuals becoming seizure-free. Similar seizure outcomes were reported in a recent meta-analysis by Fallah and colleagues [81], who analyzed 181 resections from 20 studies with a median follow-up of 2.3 years. Overall, 56 % of patients reached an Engel class I outcome, with significant negative prognosticators including generalized seizures, developmental delay, and multifocal abnormalities on electrographic or neuroimaging studies. Thus, while bilateral or multiple epileptogenic foci may make the surgical treatment of tuberous sclerosis challenging, seizure freedom can nonetheless be achieved in over half of carefully selected patients with careful preoperative evaluation.

Hemimegalencephaly and other causes of catastrophic hemispheric epilepsy

First described by Sims in 1835, hemimegalencephaly is a rare form of MCD involving abnormal proliferation of dysplastic neuronal and glial cells, leading to hypertrophy of the affected cerebral hemisphere [6, 50, 180]. It is found in approximately 0.1–0.3 % of epileptic children, but the pathogenesis remains largely unknown [50, 115]. Macrocephaly is

commonly the only physical finding in children with hemimegalencephaly, but hemigigantism and/or neurocutaneous lesions may be seen in syndromic variants [85]. Most children with this disorder develop a severe, progressive, and medically refractory epilepsy syndrome within the first 6 months of life, usually associated with marked cognitive and psychomotor impairments including contralateral hemiparesis and hemianopia [193]. Seizure types include partial motor seizures, tonic and atonic seizures, spasms, and myoclonic jerks [50, 122]. Thus far, surgical removal (anatomic hemispherectomy) or multifocal disconnection (functional hemispherectomy or hemispherotomy) of one brain hemisphere remains the most useful albeit radical treatment option for severe hemimegalencephaly to prevent further seizures, cognitive decline, and premature death [85].

Among children who receive hemispherectomy for severe hemispheric epilepsy, hemimegalencephaly accounts for 30–50 % of the cases [51, 116]. Other etiologies of catastrophic hemispheric epilepsy include Rasmussen encephalitis, Sturge–Weber syndrome, intracerebral hemorrhage, ischemic stroke, traumatic brain injury, and other cortical malformations [138]. Hemispherectomy was first described by Dandy in 1928 for glioblastoma resection and by McKenzie in 1938 for epilepsy treatment [45, 135]. In 1973, Rasmussen [159] proposed modifying the traditional anatomic hemispherectomy to reduce morbidity associated with hydrocephalus and blood loss, which at the time were thought to result from “superficial hemosiderosis.” While several variations of functional hemispherectomy or hemispherotomy have since been described, and there is some inconsistency in the use of these terms among authors, the procedure typically involves a large central resection and temporal lobectomy plus callosotomy and disconnection of the frontal and parieto-occipital residual brain [86, 138, 146, 159]. Overall, 70–85 % children who receive hemispherectomy for hemimegalencephaly or another epileptogenic hemispheric condition achieve seizure freedom [2, 50, 176]. Functional hemispherectomy is associated with comparable early seizure outcomes with less morbidity than anatomical hemispherectomy, but late seizure recurrence may be more likely with a less extensive procedure [37, 86, 98].

Moosa and colleagues [138] recently published a single-institution experience of 170 hemispherectomy procedures in children with epilepsy, representing the largest such series to our knowledge [138]. Survival analysis revealed the probability of post-surgical seizure freedom to be 76 % at 1 year and 63 % at 5 years, with 66 % of children reported as seizure-free at last follow-up (mean, 5.3 years). Bilateral PET abnormalities predicted early seizure recurrence, and there was no perioperative mortality. Complications were not investigated by Mossa et al., but are typically more common with hemispherectomy compared to more focal epilepsy resections [51]. Adverse outcomes may include worsened hemiparesis, hemianopia, or language function and the need for ventriculoperitoneal shunting [51, 86, 159]. However, because hemispherectomy is most often performed in children suffering from marked hemiparesis and hemianopia, the additional deficits incurred through surgery are generally low [51, 86, 206]. In certain cases of likely hemispheric epilepsy, one challenging decision is whether to perform focal resection only in order to limit surgical morbidity or proceed directly to hemispherectomy in order to increase the likelihood of seizure freedom. Several factors should be weighed, including severity of illness, radiographic and electrographic

findings, patient age and capacity for neural remodeling, baseline neurological deficits, and the results of family discussions. Given the progressive neurological insult caused by persistent seizures, and the greater potential for recovery in a young plastic brain, early hemispherectomy/ hemispherotomy remains a valuable treatment option in children with intractable hemispheric epilepsy.

Vascular malformations

Vascular malformations of the brain, particularly cavernous malformations and arteriovenous malformations, are commonly associated with epilepsy [71, 79]. Indications for surgical resection include the prevention of intracranial hemorrhage and/or the treatment of medically intractable seizures. While a few case reports have proposed occasional ictogenesis with other cerebral vascular malformations, such as developmental venous anomalies and capillary telangiectasia [137, 172, 185], these lesions are not typically associated with epilepsy and will not be considered further.

Cavernous malformations

Cerebral cavernous malformations (i.e., cavernomas) are endothelial-lined vascular lesions comprising dilated blood-filled sinusoids without intervening brain parenchyma and may be associated with intracranial hemorrhage [5, 149, 163]. Seizures are the most common presenting symptom of supratentorial cavernomas, likely arising from the excitotoxic effects of blood products on perilesional brain tissue [196, 200, 209]. Overall, epilepsy affects 35–70 % of patients with cavernous malformations, and about 40% of these individuals progress to pharmacoresistant epilepsy [30, 140, 170]. Most studies examining the surgical treatment of cavernomas focus on hemorrhage prevention, but clinically significant hemorrhage is not as common with these lesions as with brain arteriovenous malformations (AVMs) [124, 149, 162]. Thus, abolishing seizures is an important and often underappreciated goal in managing these lesions, given the morbid effects of intractable lesional epilepsy.

Our group performed a retrospective cohort study of 164 individuals receiving microsurgical resection of supratentorial cavernomas, of whom 62% presented with seizures and 35% had pharmacoresistant epilepsy [30]. Seizures were more common in patients with a temporal lobe lesion and, interestingly, the absence of symptomatic hemorrhage. Among the 44 patients with intractable epilepsy, 73 % were entirely seizure-free after surgery, with another 11 % reporting only rare seizures. Predictors of complete seizure freedom were gross total resection, smaller lesion diameter, and the absence of secondarily generalized seizures [30]. Comparable outcomes at other centers are reflected by a recent systematic review of 31 studies including 1,226 patients with surgically resected supratentorial cavernomas [71]. Overall, 75 % of patients were seizure-free after microsurgical resection, and modifiable predictors of this outcome included gross total resection, earlier surgical intervention, smaller lesions, preoperative seizure control with AEDs, a lack of multiple cavernomas, and a history of partial seizures only [71].

While the benefits of gross total resection in cavernoma surgery are clear, one controversy regarding extent of resection remains; that is, whether or not to excise the hemosiderin-stained parenchyma that surrounds the cavernoma, given the potential that this area may

represent the true epileptogenic zone [8, 22, 101, 184, 218, 222]. Some groups have described improved seizure outcomes with extended lesionectomy including this hemosiderin ring [8, 101, 184], while others have found no additional benefit with adding adjacent corticectomy to lesionectomy alone [30, 71, 218, 222]. Given these conflicting reports, and the theoretical potential for additional morbidity with extended corticectomy, additional prospective data regarding this issue will be important.

Arteriovenous malformations

Brain AVMs are vascular lesions comprising tortuous anastomotic arteries and veins in cerebral parenchyma without intervening capillaries, resulting in arteriovenous shunting at a central nidus [145, 208]. AVMs are the most frequent cause of intracranial hemorrhage in young adults and children [15, 167], and seizures are the second most common presenting symptom with these lesions [90, 191]. The mechanisms of epileptogenesis in AVMs are not fully known, but have been proposed to include cerebral ischemia from neighboring arteriovenous shunting, hemosiderin deposition, gliosis, demyelination, and kindling of excitatory synapses [125, 129, 191, 211, 216]. Various authors have reported the incidence of epilepsy with brain AVMs as anywhere from 12 to 57 % of patients [39, 107, 110, 118, 123, 143]. Epilepsy is more likely in patients with a history of hemorrhage, with larger lesions, and with AVM location in the temporal or frontal lobes [39, 54, 79, 104, 110, 118, 157]. Lesional epilepsy in AVM patients leads to increased morbidity [90, 191], but this is often overshadowed by the clinical focus on predicting and preventing intracerebral hemorrhage [89, 144, 150, 208].

Several case series have examined rates of seizure outcomes in the surgical treatment of AVMs causing seizures, with Engel class I outcomes reported in 49–94 % of patients [79, 107, 123, 157, 191, 217]. In a recent observational study of 440 patients with supratentorial AVMs undergoing resection at our institution, 130 (30 %) had preoperative seizures [79]. Among these patients, seizure was the presenting symptom in 98 (75 %) and led to medically refractory epilepsy in 23 patients (18 %). After a mean postoperative follow-up of 21 months, 93 % of patients with preoperative seizures achieved freedom from disabling seizures, including 91 % of those with pharmaco-resistant epilepsy [79]. Overall, seizure control is an important though undervalued goal in AVM surgery, secondary only to the prevention of devastating intracranial hemorrhage.

Commentary

Seizure freedom is frequently achieved in resective epilepsy surgery

Drug-refractory epilepsy is associated with cognitive and neuropsychological deficits and diminished quality of life [60], and a 0.5–1 % annual mortality rate [182, 190]. In contrast, epilepsy surgery is associated with only 2 % significant morbidity, such as surgical site infection or visual field deficit, and 0.24 % total surgical mortality [182, 190, 205], and longer quality-adjusted life span [34]. Outcomes are more favorable in surgery for mesial TLE surgery than focal neocortical epilepsy and vary somewhat by epilepsy etiology. The four most common distinct pathological entities found in surgical epilepsy specimens are MTS, brain tumor, MCD, and vascular malformation.

Table 3 provides a summary of seizure freedom rates and predictors across epilepsy etiologies and various subtypes. With regard to mesial TLE surgery, seizure outcome data are taken from randomized controlled trials. For other resective procedures, data reflect the findings of meta-analyses/systematic reviews of uncontrolled observational case series across the literature, where available. Overall, resective epilepsy surgery produces seizure freedom in about two thirds of patients with mesial TLE and in approximately one half of individuals with other focal epilepsy etiologies. While seizure freedom is reported more frequently in the surgical treatment of some lesions (e.g., vascular malformation, glioneuronal tumor) than others (e.g., focal MCD, glioma), direct comparison of these outcomes is precluded by an absence of prospective controlled studies and because the primary surgical goal may differ by pathology. For instance, while seizure freedom is the primary goal in surgery for MTS, seizure control may be secondary to oncologic treatment or hemorrhage prevention in glioma or AVM resection, respectively.

The importance of gross total resection and early surgical intervention

Certain predictors of seizure freedom in epilepsy surgery are commonly observed across various epilepsy etiologies (Table 3). They include MTS, gross total lesion resection, early operative intervention, localized and concordant MRI/ EEG findings, and lack of secondarily generalized seizures. Of these, extent of resection and time to surgery are potentially modifiable variables.

Subtotal lesionectomy increases not only the risk of continued seizures but also the risk of intracranial hemorrhage or oncologic progression in cases of vascular malformation or brain tumor, respectively [32, 70, 79, 188]. Gross total resection may prove challenging with a lesion involving eloquent brain or located in a region that is difficult to access surgically, but various technological tools can facilitate this surgical endeavor. In certain patients, the use of direct cortical stimulation for invasive mapping of eloquent brain – including motor, sensory, and language regions—improves the ability to safely maximize resection [29, 171]. Noninvasive neuroimaging techniques, such as white matter tract mapping with diffusion tensor imaging or functional gray matter localization with magnetoencephalography or functional MRI, may also help guide surgical planning [13, 52, 134]. The use of intraoperative MRI to facilitate more aggressive resection has also been examined, with positive results reported in one randomized controlled study of glioma surgery [177]. Similarly, intraoperative MR angiography or invasive cerebral angiography has been proposed to guide complete microsurgical obliteration of AVMs, but these techniques have not been evaluated prospectively [10, 56]. Nevertheless, despite the positive prognostic value of extent of resection in lesional epilepsy surgery, patient safety remains the primary surgical concern, and *primum non nocere* the guiding principle.

Early surgical intervention in drug-resistant epilepsy is associated with an increased likelihood of postoperative seizure freedom, and seizure freedom is the single most important predictor of quality of life in epilepsy [55, 132]. Early intervention is also important, however, to reduce the duration of persistent epilepsy and its damaging effects on the brain. Pharmacoresistant epilepsy is associated with progressive neuropsychological and cognitive deficits [60, 68, 105], a 0.5–1 % annual mortality rate, and a lifetime standardized

mortality two to three times higher than the general population [182, 190, 205]. In contrast, resective epilepsy surgery is associated with approximately 2 % significant morbidity and 0.24 % total surgical mortality [182, 190, 205], as well as improvement in overall life span, neuropsychological profile, and quality-adjusted life years [34, 197, 201]. With temporal lobectomy, the value of early surgical intervention has been validated by class I evidence as newly refractory TLE patients experience significantly improved seizure outcomes with early surgery compared to continued medical therapy [61]. Furthermore, it is now well established that focal epilepsy patients are unlikely to achieve seizure freedom with medication alone after the failure of two or more separate AED regimens, leaving little reason to delay surgical evaluation [61, 102, 126, 127]. Thus, evidence-based practice guidelines strongly encourage early referral of children and adults with epilepsy to a comprehensive epilepsy center for multidisciplinary medical and surgical evaluation [41, 62, 63, 128].

Limitations

The goal of this manuscript was to provide a brief but broad overview of seizure freedom rates and predictors in resective epilepsy surgery by pathological entity. While a detailed examination of other endpoints in the surgical treatment of epilepsy —neuropsychological and cognitive outcomes, quality of life assessments, surgical complication rates, patient satisfaction, and medication discontinuation—is beyond the scope of this focused review, they remain critical considerations. Although we did not consider non-resective surgical therapies in this review, such as callosotomy or device implantation, these remain important palliative treatment options for individuals who are not candidates for definitive resection. Similarly, while alternative treatment options exist for some lesions discussed herein (e.g., stereotactic radiosurgery or endovascular embolization of an AVM), they are beyond the scope of our present focus. Next, a bias toward our own institutional proceedings is present in this review, intended to reflect our group’s treatment experiences. However, a thorough and comprehensive evaluation of the literature was performed to ensure that our clinical results are comparable to those of other groups, and differences are described where applicable. Finally, only temporal lobectomy outcomes have been evaluated by randomized controlled trials, and all other results discussed here are the product of uncontrolled observational case series and, therefore, inherently prone to bias. Randomized controlled trials evaluating the efficacy of resective epilepsy surgery in focal neocortical epilepsy are critically needed.

Conclusions

Resective epilepsy surgery is a safe and effective treatment for patients with drug-resistant epilepsy harboring a localizable seizure focus. Surgery leads to seizure freedom in approximately two thirds of patients with mesial TLE and about one half of individuals with focal neocortical epilepsy, with the former statistic validated by two randomized controlled trials. While several factors are associated with seizure outcome in epilepsy surgery, two modifiable predictors of seizure freedom include early operative intervention and, in patients with a discrete lesion, gross total resection. Practice guidelines recommend that epilepsy patients experiencing persistent seizures after two or more medication trials should be

referred to a comprehensive epilepsy center for multidisciplinary evaluation, including surgical consideration.

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Table 1

Histopathological findings in 4,512 patients with focal intractable epilepsies

Entity	Variant ^a	Number	Mean age at Surgery (years)	Hemisphere	Gender	Mean age at onset (years) ^b	Mean duration (years) ^c
Mesial temporal sclerosis		1,591	34.6	659 L/611 R	786 M/805 F	11.5	23.3
Tumor		1,236	28.5	407 L/397 R	638 M/565 F	16.5	12.8
	Ganglioglioma	570	25.4	184 L/158 R	285 M/263 F	12.7	13.5
	DNET	189	26.3	59 L/68 R	105 M/84 F	15.2	12.3
MCD		577	18.5	228 L/242 R	299 M/276 F	5.6	12.4
	FCD I	66	11.5	35 L/26 R	16 M/33 F	3.5	7.2
	FCD II	216	18.4	76 L/96 R	112 M/104 F	4.1	14.1
Vascular malformation		271	36.4	91 L/108 R	157 M/114 F	23.5	13.4
Dual pathology		218	24.8	78 L/112 R	127 M/91 F	9.7	14.6
Scar/gliosis		239	25.2	92 L/91 R	147 M/90 F	10.3	14.8
Encephalitis		73	22.0	26 L/29 R	43 M/29 F	13.9	9.4
No lesion		307	29.2	117 L/58 R	161 M/146 F	12.7	16.1

All data were obtained from the German Neuropathological Reference Center for Epilepsy Surgery. Reproduced with publisher and author permission from Blumcke [18]

FCD focal cortical dysplasia, DNET dysembryoplastic neuroepithelial tumor, MCD malformation of cortical development

^aFrequent variants of specific entities are highlighted

^bMean age at onset of spontaneous seizure activity

^cMean duration of seizure disorder before surgical treatment

Table 2

Three-tiered ILAE classification system of FCD distinguishes isolated forms (FCD types I and II) from those associated with another principal lesion (FCD type III)

FCD type I (isolated)	Focal cortical dysplasia with abnormal radial cortical lamination (FCD type Ia)	Focal cortical dysplasia with abnormal tangential cortical lamination (FCD type Ib)	Focal cortical dysplasia with abnormal radial and tangential cortical lamination (FCD type Ic)	
FCD type II (isolated)	Focal cortical dysplasia with dysmorphic neurons (FCD type IIa)		Focal cortical dysplasia with dysmorphic neurons and balloon cells (FCD type IIb)	
FCD type III (associated with principal lesion)	FCD type III (associated with principal lesion)	Cortical lamination abnormalities in the temporal lobe associated with hippocampal sclerosis (FCD type IIIa)	Cortical lamination abnormalities adjacent to a glial or glioneuronal tumor (FCD type IIIb)	Cortical lamination abnormalities adjacent to vascular malformation (FCD type IIIc)

FCD type III (not otherwise specified): if clinically/radiologically suspected principal lesion is not available for microscopic inspection. Please note that the rare association between FCD types IIa and IIb with hippocampal sclerosis, tumors, or vascular malformations should not be classified as FCD type III variant. Reprinted with permission from Blümcke et al. [19]

Table 3

Seizure freedom and outcome predictors in resective epilepsy surgery

Epilepsy etiology/cause	Specific pathology	Engel class I outcome	Predictors of favorable outcome	References included
Mesial temporal lobe epilepsy	Mesial temporal sclerosis and other causes	58–73 % ^a	Febrile seizures, mesial temporal sclerosis, abnormal MRI, tumor, EEG/MRI concordance	[61, 63, 194, 207]
Tumor	Glioneuronal tumor	72–80 % ^b	Early intervention, gross total resection, lack of generalized seizures	[67, 214]
	Low grade glioma	67 % ^b	Gross total resection, early intervention	[66]
Malformation of cortical development	Focal cortical dysplasia	58 % ^b	Gross total resection, lack of generalized seizures, temporal location, abnormal MRI, type II classification	[168]
	Tuberous sclerosis	56–57 % ^b	Lack of intellectual disability, lack of generalized seizures, localized ictal EEG, EEG/MRI concordance	[81, 114]
	Severe hemispheric epilepsy (hemispherectomy)	66–85 % ^c	Early intervention, young age, Sturge–Weber, lack of hemimegalencephaly, unilateral PET abnormality	[2, 138, 176]
Vascular malformation	Cavernous malformation	75 % ^b	Gross total resection, early intervention, small lesion, single lesion, lack of generalized seizures	[71]
	Arteriovenous malformation	70–91 % ^c	Early intervention, young age, gross total obliteration, lack of deep artery perforators	[79, 191, 217]

^aData obtained from randomized controlled trial^bData obtained from systematic reviews and meta-analyses (where trial data are not available)^cData obtained from at least three large case series (where meta-analysis data are not available)