SURGICAL MANAGEMENT OF DRUG-RESISTANT FOCAL EPILEPSY

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Epilepsy surgery is underutilized in patients with focal seizures refractory to appropriate antiepileptic drug (AED) trials consisting of two or more medications. Two small randomized controlled trials clearly established superiority of epilepsy surgery compared to continued medical treatment. Nine systematic reviews, in addition to two large case series, summarize an abundance of retrospective case series that report seizure freedom in 34%-74% of patients, with a median of 62.4%. The remainder of systematic reviews and meta-analyses examines subpopulations. Patients with extratemporal and/or non-lesional epilepsy benefit less than patient with temporal epilepsy or obvious MRI abnormalities. Children benefit equally from surgery as evidence by several meta-analyses. The most beneficial type of procedure such as anterior temporal resection versus a selective amygdalohippocampectomy are still under discussion, as anterior temporal lobe resection seems to have a mild benefit in terms of seizure freedom, but neuropsychological consequences are less well studied. Other outcomes beyond seizures are less well documented. Left temporal resections are associated with a risk for verbal memory and confrontation naming, other cognitive domains are less documented or not clearly measured by standard testing. Mortality is low and the most reported neurological morbidity is visual field defects after temporal lobe resection. Quality of life improves after surgery, especially in seizure-free patients.

INTRODUCTION:

The prevalence of active epilepsy in the US is estimated by the Center of Disease control to be 8.4/1000 persons[1]. Approximately 30-35% of patients with seizures have drug-resistant epilepsy[2], which is considered having failed two antiepileptic medications at tolerated, appropriately chosen doses to sustain seizure freedom[3]. Numerically there live more than 750 000 persons in the US with drug resistant epilepsy, but only 1500 epilepsy surgeries are performed yearly in the US[4]. Published practice parameters in 2003 by the American Academy of Neurology “strongly” recommended referral to an epilepsy center for surgical consideration if seizures are drug-resistant. However, this barely had an influence on referral patterns and did not majorly increase the number of surgeries performed [5]. There is a possibility that epilepsy surgery remains underutilized as outcome measures mainly focused on seizure outcome in the past. Other outcome variables such as cognition, psychiatric disability, and psychosocial impact are rarely reported but may influence referrals and utilization of surgery. This article provides an update on the best available evidence for the effectiveness of resective epilepsy surgery, including associated morbidity and mortality and non-seizure related outcomes to enhance the understanding of the effectiveness of epilepsy surgery.

RESULTS:

Two randomized controlled trials in temporal lobe epilepsy unequivocally established that surgical therapy is more effective than medical treatment. Both studies are limited by the small number of patients enrolled. Seizure freedom was achieved at 1 year in 58% of patients compared to 8% with medical treatment ($p<0.001$)[6]. Seizure freedom for treatment of drug-resistant epilepsy within two years of onset was achieved in 73% with surgery, as compared to 0% in medical patients at 2 years ($p<0.001$), but this study only included 38 participants[7]. The study closed due to insufficient patient accrual. Both studies included only temporal lobe epilepsy and excluded extratemporal syndromes.

There is an abundance of observational cohort studies reporting postoperative seizure outcome. Only few observational studies report on control groups that received medical treatment[8,9]. Seizure freedom in patients with all types of focal epilepsy is reported between 34-76 % with a median of 62.5% (table 1). The effect seems sustained over long term with mild reductions in seizure-free proportion of patients over prolonged follow up [10-12]. A prolonged follow up study in temporal lobe epilepsy reported 48% seizure freedom after 26 years[12]. Studies use varying outcome measures, most frequently the Engel outcome classification or the ILAE outcome scale (supplementary material), but not infrequently define their own outcome scale[13,14]. Kaplan Meier Analysis to time to first seizure and cumulative probability of remission are alternative outcome measures[6,13,15].

Surgical localization: Previous systematic reviews stressed that data is insufficient to establish the efficacy of extratemporal epilepsy surgery[16,17]. Overall rate of seizure freedom are lower in studies and reviews of extratemporal lobe epilepsy as compared to temporal lobe epilepsy [10,16,18,19] but not necessarily significantly different as reported in some studies[13,15,20-23] and to the contrary in others[24]. Frontal lobe surgery is more the

commonly approached extratemporal surgery as compared to occipital or parietal resections[10]. A large meta-analysis of nearly 1200 patients with frontal lobe epilepsy reports a Class I seizure free outcome in 45.1%[25], and subpopulations of parietal-occipital epilepsy are reported with seizure freedom in 46%[10].

Pathology findings: Various reviews and meta-analyses report on specific pathologies and their seizure outcomes [13,14,19,21-24,26-30], there is consistency that benign tumors and hippocampal sclerosis seem to associated with a more favorable outcome[13-15,23,27]. The largest systematic review of observational studies reports an Odds ratio of 0.58 (CI 0.35-0.64) and tumors of 0.52 (0.42-0.80) in favor of those pathologies[24]. Other pathologies were not significantly associated with better outcome. Surgery in tuberous sclerosis increasingly becomes the treatment of choice and success rates are similar to other pathologies[29-31].

MRI findings: There is consensus that lesional or MRI positive epilepsy is associated with a better outcome than non-lesional epilepsy in large systematic reviews and meta-analyses[25,32,33].

C**onclusion**: epilepsy surgery is highly effective and should be offered to patients if seizures do not respond to medications. Consultations at specialized epilepsy centers are the necessary prerequisite for optimal care for those patients. The epilepsy community needs to shift attention from seizures alone to other outcomes such as cognition and psychosocial outcome.

Surgical Treatment of Epilepsy: Final Points

1) Approximately 30% of all patients with epilepsy will have physically, socially, and medically disabling seizure disorders. Patients with intractable epilepsy are at increased risk for serious morbidity and mortality. Most individuals who will respond favorably to antiepileptic drug medication are successfully treated with the initial management. Patients who "fail" two (2) antiepileptic drug medications used appropriately are likely to have a medically refractory seizure disorder and should be investigated for alternative forms of treatment. Potential treatment options include:
   a) Antiepileptic drug medication
   b) Vagus Nerve Stimulation
   c) Surgical Treatment
   d) Combination of above

2) A comprehensive evaluation is necessary in the patient with intractable epilepsy. Patients should be referred to neurologists with a subspecialty expertise in epilepsy at a comprehensive epilepsy center with the necessary subspecialty resources and personnel. This includes video-EEG monitoring to classify seizure-type or localize the site of seizure onset, or both. All patients should undergo an MRI head. A focal cortical resection is the most effective treatment for intractable partial epilepsy. Surgically remediable epilepsy syndromes have been identified including medial temporal lobe epilepsy and lesional epilepsy. Approximately 60-80% of patients with partial epilepsy are rendered seizure-free with a temporal lobe resection. An anterior temporal lobectomy is the most common operative procedure for intractable partial epilepsy. Patients who are potential surgical candidates may require advanced neuroimaging studies including:
   a) Positron emission tomography (PET)
   b) Ictal Single Photon Emission Computed Tomography (SPECT)
   c) Magnetic resonance Spectroscopy (MRS)
   d) Patients with medically disabling seizure disorders are at increased risk for serious morbidity and mortality, including cognitive disorders, depression, physical trauma, and sudden death in epilepsy (SUDEP). The goals of treatment for individuals with drug-resistant epilepsy are to render the patient seizure-free, avoid treatment-related adverse effects, and allow the individual to become a participating and productive member of society.

   e) Most individuals who will respond favorably to antiepileptic drug (AED) medication are successfully treated with the initial management in the first two years. Patients who do not respond favorably to two AED medications used appropriately are likely to have drug-resistant epilepsy and should be investigated for alternative forms of treatment, including surgery.

f) Surgical therapy is an important and underutilized treatment in patients with drug-resistant focal epilepsy. Surgical procedures for epilepsy range from focal resection of the epileptogenic cortex (anterior temporal lobectomy, focal cortical resection) to interventions that remove or isolate the cortex of a grossly diseased hemisphere (functional hemispherectomy, multiple subpial transections, and anterior corpus callosotomy). The latter procedures are primarily performed in children and are not discussed further here. In general, only complete resection of the epileptogenic brain region offers the chance of long-term seizure freedom.

SURGICAL CANDIDATES — Focal cortical resective surgery is a consideration in patients with drug-resistant focal epilepsy if the seizures emanate from a region that can be removed with minimal risk of disabling neurologic or cognitive dysfunction.

g) The localization of seizure onset, underlying surgical pathology, and seizure type(s) are important determinants of surgical candidacy. The most favorable candidates are those with MRI-identified substrate-directed abnormalities that indicate both the pathological findings underlying the epileptic brain tissue and the surgical localization of seizure onset. Such MRI findings, together with concordant EEG data, are pivotal in selecting operative candidates and determining the strategy for the surgical procedure.

h) In adults, there are three major types of seizure disorders that may be remedied with focal cortical resective surgery:

- Patients with medial temporal lobe epilepsy and localization of the epileptogenic zone in the amygdala and hippocampus are the most common candidates for effective surgical therapy. As discussed below, observational data and a single completed randomized, controlled trial support the superiority of surgical therapy compared to continued AED medication for patients with drug-resistant temporal lobe epilepsy.

- Patients with lesional epilepsy due to focal structural pathology such as a low-grade glial tumor, vascular malformation, or malformation of cortical development (MCD) at risk for medically refractory seizures and may also be good surgical candidates. There are important differences in the likelihood of surgical success depending on the specific pathological finding, however; the operative outcome is distinctly less favorable in individuals with focal cortical dysplasia and other MCDs.

- Patients with drug-resistant focal epilepsy and a normal brain MRI are more challenging, but some of these patients are nonetheless good surgical candidates. Localization of the epileptic brain tissue in these patients often requires chronic intracranial EEG monitoring in addition to functional and metabolic imaging techniques.

i) Patients who are typically not surgical candidates for focal cortical resection include individuals with bilateral or multifocal onset of focal seizures, those with significant medical comorbidities that preclude the operative procedure, and patients with generalized epilepsy. Patients in whom the site of seizure onset and initial seizure propagation is intimately associated with functional cortex may also not be appropriate candidates for resective surgery.

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