

Surgical management of epilepsy

J M N Enslin,¹ BPhysT, MB ChB, FCNeurology (SA), MMed (Neurology); S J Rothmeyer,² MB ChB, FCNeurology (SA); A G Fieggen,³ MB ChB, MSc, MD, FCNeurology (SA)

¹ Division of Neurology, Red Cross War Memorial Children's Hospital, and Constantiaberg Mediclinic, Cape Town, South Africa

² Department of Neurology, Faculty of Health Sciences, Groote Schuur Hospital and University of Cape Town, South Africa

³ Department of Neurology, Faculty of Health Sciences, University of Cape Town, and Division of Neurology, Red Cross War Memorial Children's Hospital, Cape Town, South Africa

Corresponding author: J M N Enslin (enslin@functionalneurology.co.za)

The fact that epilepsy can be cured or ameliorated with surgery is an often neglected and overlooked aspect of modern management. Epilepsy affects almost 50 million people worldwide. One-third of people who suffer from epilepsy are refractory to medication alone. It is this group of patients who may benefit from epilepsy surgery, which can be divided into three main categories, i.e. resection procedures, disconnection procedures, and neuromodulation procedures. The goal of surgery in epilepsy is to remove the epileptogenic region from the brain, or to disconnect it and thereby prevent spread to other parts of the brain. In cases where this is not possible owing to the location of the epileptic focus, certain neuromodulation techniques may benefit the patient. Successful outcomes of epilepsy surgery techniques vary from 50% to 80% in rendering patients free of their epilepsy; many more patients can expect improvement in the severity or frequency of their disabling seizures. The outcome depends on factors such as age, location of the epileptogenic zone, histology and cause of the seizures. Patients undergo a detailed and prolonged work-up to determine candidacy and to decide on the safest technique that will lead to the best outcomes. An experienced team should perform the surgery. This team should consist of multiple members who can attend to the medical, social, psychological and reintegration needs of the patient before and after surgery.

S Afr Med J 2016;106(8):757-760. DOI:10.7196/SAMJ.2016.v106i8.11194

Epilepsy is the fourth most common disorder that affects the nervous system, with only migraine, cerebrovascular incidents and Alzheimer's disease being more common. Epilepsy affects ~50 million people worldwide.^[1] In Africa, epilepsy affects ~10 million people.^[2] Global statistics show that about one-third of patients with epilepsy are refractory to anti-epileptic medication.^[3] This translates into ~2.5 million people in Africa with devastating epilepsy, who may require alternative treatment to control or cure their epilepsy.

Since 1886, neurosurgeons such as Horsley, Penfield and Krause have been interested in the surgical treatment of epilepsy in both adults and children.^[4] From these early days, doctors understood that epilepsy is caused by abnormal electrical discharges in a specific part of the brain. This led to the premise that if that abnormal part of the brain can be resected, the epilepsy will be controlled.

Indications for surgery

Surgery should be the main therapeutic option in refractory epilepsy if a clear cause has been identified. This is the case in patients with focal cortical developmental or migrational abnormalities, and in patients in whom epilepsy is associated with a tumour or lesion in the brain. Undertaking surgery is a much more difficult decision in patients with cryptogenic epilepsy, i.e. where there is no anatomical abnormality demonstrable on a magnetic resonance imaging (MRI) scan. At this point, the role of the functional neurosurgeon specialising in epilepsy surgery and working in conjunction with an experienced epileptologist (neurologist with a special interest in epilepsy) becomes vital. Surgery for epilepsy is never an emergency, except in rare cases of rapidly enlarging brain tumours, but then the focus is on tumour surgery and not treating the epilepsy. The timing of surgery in the course of the disease also needs some consideration, with the benefit of earlier surgery becoming more evident from recent data. It has been demonstrated that earlier control of seizures (at a younger age) leads to better long-term outcomes in patients with epilepsy.^[5,6]

For a patient with epilepsy to be considered for work-up for surgery, the following criteria must be met:

- The patient must be *refractory to medical treatment*, i.e. the patient must be on adequate medical therapy with at least two drugs, one of which is a newer-generation agent that is monitored and prescribed by an experienced epileptologist, and have life-impairing seizures.^[7] There is no time duration to this definition.
- There must be *correlation* shown between *semiology* (clinical presentation, e.g. posturing, during an attack), *anatomy* (imaging findings on an MRI scan) and *electrical* (findings on an electroencephalogram (EEG) tracing) abnormalities.

Work-up for surgery

The work-up in a patient with epilepsy, who is a potential candidate for surgery, requires a multidisciplinary approach. Patients with significant epilepsy are usually managed by an epileptologist (a paediatric neurologist, or an adult neurologist with a special interest and experience in treating patients with epilepsy). The team must be convinced that the patient is on optimal medication to prove refractoriness before surgery is considered. Pre-operative neuropsychological testing can help in determining the side of dominance of speech and memory and the psychological impairment, and prepare the family for significant changes if the surgery is successful. It seems odd to be concerned about this, but for a family with a patient with a chronic illness such as epilepsy, the patient not having epilepsy often leads to greater anxiety and is a challenge. Therefore, meticulous psychological follow-up and preparation are of the utmost importance. The neurosurgeon takes part in the counselling and evaluation of the patient and the interpretation of the multimodality imaging and telemetry to plan the surgery.

Careful telemetry is needed, while the patient is kept in a unit with constant 24-hour per day video surveillance and is connected to the EEG monitor for the entire period, sometimes for a few days.

This allows accurate correlation between the ictus (seizure event), clinical presentation (semiology) and EEG of the patient during the event. The patient undergoes neuro-imaging to illustrate the cortical abnormality that may be associated with the epileptiform area. Currently, 3 Tesla MRI scanning is becoming the gold standard for the imaging of patients with epilepsy, as it allows the epilepsy surgery team to evaluate for subtle cortical abnormalities that were previously left undetected by 1.5 Tesla scanners. Special sequencing, such as diffusion tractography imaging and functional MRI, can be used to determine the association between eloquent brain areas and the epileptogenic area, thereby allowing preservation of function in patients who undergo resection of the epileptiform area. Some epilepsy surgery units have access to positron emission tomography (PET) scanning that allows visualisation of abnormal activity or active lesions in cases of multiple lesions, e.g. patients with tuberous sclerosis, hereby determining which lesion is responsible for the seizures. Combining pre-ictal and ictal single-photon emission computed tomography (SPECT) scans can also be very helpful in localising the epileptiform cortex, especially in patients in whom there is no structural abnormality detectable on MRI. The intracarotid injection of amobarbital (Wada test) has mostly been replaced by functional MRI, which offers a non-invasive way to determine lateralisation of functions such as speech and memory. This is especially important in temporal lobectomies. A CT scan has limited use in the work-up of refractory epilepsy, but is often still the first imaging modality employed owing to the cost associated with MRI scanning.

Surgical procedures

The goal of surgery is always maximal resection of the epileptiform focus, tempered by the need to respect and preserve functional areas, venous drainage, arterial supply and white matter connecting tracts.

Surgery for epilepsy is divided into three major categories:

- anatomical resection procedures, e.g. resection of the frontal lobe or temporal lobe
- disconnection procedures (disconnecting the epileptiform cortex from the rest of the brain by sectioning white matter tracts)
- neuromodulation (placing of vagal nerve stimulator or deep brain stimulation for epilepsy).

Resection techniques

The choice of resection techniques, or combinations thereof, depends on the location of the epileptiform focus, eloquent tissue, vascular supply, and venous drainage patterns. Surgical planning is also informed by only grey matter (cerebral cortex) having epileptogenic potential; however, seizure activity can propagate via white matter tracts. Resective techniques remove the offending area or lesion, often also with a subcortical bank of tissue, whereas disconnective techniques tend to leave the area of epileptogenic grey matter as an isolated island in the brain.

Certain types of epilepsy are better controlled with specific techniques, e.g. atonic seizures (drop attacks) are ideal cases for corpus callosotomy, as this prevents generalisation to the contralateral cortex. Patients continue to have unilateral seizure activity, but not the dangerous atonic seizure that often leads to falling into a fire or in front of a moving vehicle. In eloquent areas the surgeon uses a subpial dissection technique, where the pial bank is preserved against blood vessels and nerves, while the grey matter is dissected out and away from the white matter tracts, often using an ultrasonic aspirating device on very low suction and fractionation settings. An area of white matter network, which is free of the electrically active grey matter, is left behind. Electrical mapping techniques are used during the

procedure to preserve eloquent brain matter. In this way the delicate border between eloquent tissue and epileptiform tissue is delineated, allowing safe resection.

It is important to stress the difference between tumour surgery and epilepsy surgery. In tumour surgery the focus is on removing the lesion and the malignant infiltrates in the surrounding tissue, which are often not visible under a microscope. Various techniques are used to allow visualisation of this infiltrated area, e.g. amino-acid PET masking. Traditionally, this approach is used in epilepsy surgery associated with lesions, such as developmental neuro-ectodermal tumours. The belief is that the lesion is epileptogenic; therefore, performing a lesionectomy is all that is required to control the seizures. However, epilepsy surgeons are aware that, in some cases, this does not control the epilepsy (Figs 1 and 2 illustrate this principle). Part of the work-up for epilepsy surgery takes this into account and great effort is made to search for the epileptiform cortex, even more distant from the lesion. This is why in epilepsy surgery the term topectomy is preferred rather than lesionectomy.

Disconnection techniques

In patients in whom the focus of the epileptiform activity is restricted to an area that does not allow resection owing to its eloquence, another approach is to 'disconnect' that part of the brain from the rest, thereby in effect isolating the epileptic activity to a focal portion of the brain and preventing secondary generalisation. An example of this is a functional hemispherectomy, where the diseased hemisphere is disconnected from the rest of the brain and the patient does not have dangerous progression of focal seizures to generalised seizures. This procedure is a variation of the older technique of anatomical hemispherectomy, where one half of the brain was removed. This led to significant morbidity and mortality.

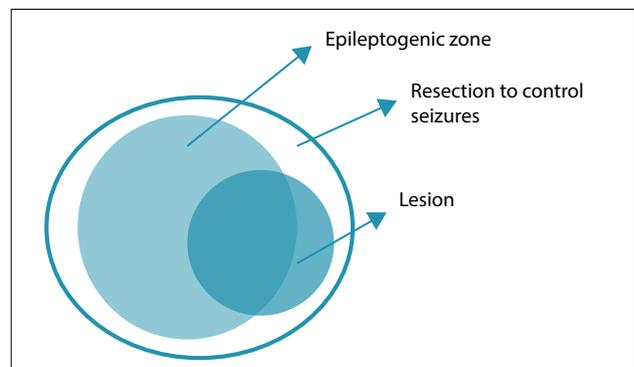


Fig. 1. Relationship between lesion and resection margins that may be required to control seizures.

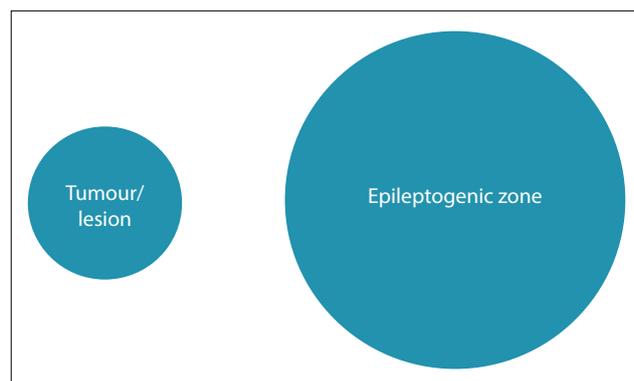


Fig. 2. Resecting of a lesion may not always cure epilepsy.

Neuromodulation techniques

Neuromodulation for epilepsy is being investigated, as it is seen as the next great frontier in epilepsy surgery. In the same manner that deep brain stimulation has been shown to have a significant effect in patients with Parkinson's disease, dystonia and tremor, certain targets in the thalamus show promise in treating medication- and surgery-refractory epilepsy. Vagal nerve stimulation is a surgical procedure in which a small wrap-around electrode is placed on the left vagal nerve in its cervical course. This electrode is then connected to an implanted pulse generator, similar to a cardiac pacemaker, which stimulates the vagal nerve at a predetermined frequency and amplitude. The mechanism of action is as yet unsure, but it does show at least a 50% improvement in 50% of patients who have the device implanted.^[5] It seems as though only a small number of patients benefit, but it is important to remember that this group of patients suffer tremendously and that medication and other surgical options have failed or are not possible. Therefore, even such small odds are worthwhile and can lead to great improvement in quality of life. Some of the more recent trials are related to deep brain stimulation (DBS) for drug-resistant epilepsy.^[8] In this procedure a DBS electrode is placed into the anterior nucleus of the thalamus via a stereotactic technique and an implanted pulse generator produces a constant pulse at a predetermined frequency, which modulates abnormal electrical activity in the brain. More recently, promising work has been done, where a subdural or depth electrode and a thalamic electrode are implanted into the epileptic zone in the brain. As soon as abnormal electrical activity is detected in a closed loop system, the pulse generator stimulates the thalamus and the abnormal electrical activity is aborted.^[9] This technique is still in its infancy as a treatment for medical refractory epilepsy, but holds great potential, especially for non-lesional epilepsy or epilepsy with seizure foci that are in non-resectable areas.

Surgical risks for epilepsy

Surgery for epilepsy is a major decision and there are significant associated risks. Therefore, strict criteria need to be met before surgery can be considered in the treatment of medical refractory epilepsy. Surgery can lead to memory impairment after temporal lobectomies, and motor weakness or aphasia in hemispheric procedures. Occipital lobe surgery and damage to the optic tract in medial temporal lobe resections can lead to blindness. Disturbances in the flow of cerebrospinal fluid can lead to hydrocephalus that will require shunt procedures, with associated risks.

These risk factors need to be weighed up against those associated with the long-term use of anti-epileptic medication. Females, especially, have to consider the teratogenic effect of most first-line anti-epileptic medication during pregnancy. Untreated epilepsy carries significant morbidity and even mortality. Sudden unexpected death in epilepsy is a rare, but real threat to patients with the condition.

There are therefore certain conditions, such as focal cortical dysplasia and dysembryoplastic neuro-epithelial tumours, which are known to be mostly refractory to anti-epileptic drugs, where an argument can be made to perform the respective surgery as soon as

a diagnosis is made, especially if the lesion is in a non-eloquent area, such as the medial temporal lobe in the right hemisphere.

Outcomes of epilepsy surgery

In the follow-up of patients after epilepsy surgery it is important to enquire about seizures and their frequency. For many years the emphasis of epilepsy surgery outcomes has focused on these aspects, but increasingly units are publishing their data on patients with regard to their memory, school performance, and psychological and emotional wellbeing.^[10] Fewer seizures is only half of the problem solved, as 45 - 50%^[10] of patients suffer from depression and anxiety after surgery and careful evaluation is needed to determine sequelae of the resected cortical tissue and its effect on mood, memory and personality, with school and work performance being sensitive surrogates to evaluate this. In the absence of seizures, patients have difficulty in dealing with these new feelings of depression and emotional lability. The treating team need to be aware of this and preempt these factors during counselling.

Freedom of seizures after surgery is the primary goal, though. The outcome is dependent on the aetiology of the seizure, location of the epileptiform region, degree of resection done and type of procedure performed. Some published epilepsy surgery outcomes are summarised in Table 1.^[11-13] There are some factors that have been identified to yield better long-term seizure freedom after surgery, e.g. presence of hippocampal atrophy and absence of generalised tonic-clonic seizures. Spencer *et al.*^[14] found that 25% of patients relapse after 2 years of seizure freedom in cases of temporal lobe resections. Patients with medial temporal lobe epilepsy, who are operated on later in life, also show a worse seizure freedom rate after surgery.^[15] This is yet another motivation for earlier surgery in patients who are medically refractory to epilepsy treatment.

Children with epilepsy and a specific lesion on MRI are also increasingly free of seizures after surgery compared with those with no identifiable lesion – only an electrically localisable focus (70% v. 56% in a temporal focus). The seizure freedom rate in non-lesional epilepsy is about 62%, independent of the presence of a lesion.^[16] In a study by the University of California, Los Angeles (UCLA) group^[17] it was shown that children with cortical dysplasia have a slightly higher recurrence rate than other patients with epilepsy, but it is clear that early surgery, before 3 years of age, makes a significant difference and leads to lower seizure recurrence rates. In a comparison of children with cortical dysplasia and surgery before 3 years of age v. older children, the younger group showed 65% seizure freedom compared with 38% in the older group at 5 years after epilepsy surgery follow-up.^[17]

Even though more than half of patients remain seizure free after surgery, the trend in our unit and most of the rest of the world is to taper the anti-epileptic medication slowly 6 months after surgery. Most patients (95%) who are seizure free at 6 months after surgery remain seizure free thereafter.^[18]

Table 2 summarises possible causes of seizure recurrence after successful surgery.^[19,20] Careful multidisciplinary follow-up and counsel-

Table 1. Summary of epilepsy surgery outcomes^[11-13]

Adults	Temporal epilepsy	Extratemporal epilepsy	Extratemporal lesion	Frontal seizures
Seizure free after 1 year, %	68	45	67	23
Significant improvement, %	24	35	23	32
Seizure free at 1 year	Temporal epilepsy	Extratemporal epilepsy	Hemispherectomy	All surgeries
Children, %	74	58	67	67
Adolescents, %	80	52	75	69

Table 2. Early and late seizure recurrence causes^[19,20]

Early	Late
Incomplete resection of epileptogenic zone	Incomplete resection of epileptogenic zone
Acute AED level changes	Gliosis of the resection margins
Electrolyte disturbances/hypoglycaemia	Progression of underlying disease or tumour
Fever/pain/sleep deprivation	Withdrawal of AEDs in multifocal epilepsy
Surgery-related cortical irritation	
AED = anti-epileptic drug.	

ling is an ongoing process and the patient is never completely discharged – support and motivation continue life-long.

Summary

Surgery for medical refractory epilepsy requires a multidisciplinary approach that involves neurosurgeons, epileptologists, neuropsychologists and a keen team of nursing and social worker staff. With the premise that about 2.5 million people in Africa have medically refractory epilepsy that may be treated with surgery, a great deal of awareness needs to be spread among physicians, nursing personnel and families of patients with severe epilepsy. Early surgery in patients with localisable seizure foci in non-eloquent areas such as the medial temporal lobe leads to significant reductions (>70%) in epilepsy.

Epilepsy is one of the most disabling chronic diseases; if help is possible, it must

be made available to those who need it. With the increasing amount of knowledge, imaging methods and surgical techniques gained every year, surgery for epilepsy can be done safely and produce reliable results. Ultimately, the quality of life of patients with this devastating disease can be greatly improved. Timely referral to specialist epilepsy surgery units is mandatory if we want to decrease this disease burden on patients and their families.

References

1. Dua T, de Boer HM, Prilipko LL, Saxena S. Epilepsy care in the world: Results of an ILAE/IBE/WHO global campaign against epilepsy survey. *Epilepsia* 2006;47(7):1225-1231. DOI:10.1111/j.1528-1167.2006.00595.x
2. World Health Organization. The Global Campaign Against Epilepsy. Epilepsy in the African Region: Bridging the Gap. Geneva: WHO, 2004.
3. Schuele SU, Lüders HO. Intractable epilepsy: Management and therapeutic alternatives. *Lancet Neurol* 2008;7(6):514-524. DOI:10.1016/S1474-4422(08)70108-X
4. Magiorakis E, Diamantis A, Sidiropoulou K, Panteliadis C. Highlights in the history of epilepsy: The last 200 years. *Epilepsy Res Treat* 2014;2014:1-13. DOI:10.1155/2014/582039
5. Mapstone TB. Vagus nerve stimulation: Current concepts. *Neurosurg Focus* 2008;25(3):E9. DOI:10.3171/FOC/2008/25/9/E9

6. Chen H-H, Chen C, Hung S-C, et al. Cognitive and epilepsy outcomes after epilepsy surgery caused by focal cortical dysplasia in children: Early intervention may be better. *Child's Nervous System* 2014;30(11):1885-1895. DOI:10.1007/s00381-014-2463-y
7. Engel J, Wiebe S, French J, et al. Practice parameter: Temporal lobe and localized neocortical resections for epilepsy. *Neurology* 2003;60(4):538-547. DOI:10.1212/01.WNL.0000055086.35806.2D
8. Fisher R, Salanova V, Witt T, et al; SANTE Study Group. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia* 2010;51(5):899-908. DOI:10.1111/j.1528-1167.2010.02536.x
9. Sun FT, Morrell MJ, Wharen RE. Responsive cortical stimulation for the treatment of epilepsy. *Neurotherapeutics* 2008;5(1):68-74. DOI:10.1016/j.nurt.2007.10.069
10. Ring HA, Moriarty J, Trimble MR. A prospective study of the early postsurgical psychiatric associations of epilepsy surgery. *J Neurol Neurosurg Psychiatry* 1998;64(5):601-604. DOI:10.1136/jnnp.64.5.601
11. Rasmussen T. Surgery for frontal lobe epilepsy. *Adv Neurol* 1975;8:197-205.
12. Engel J Jr. Update on the surgical treatment of the epilepsies. *Neurology* 1993;43(8):1612-1617. DOI:10.1212/WNL.43.8.1612
13. Wyllie E, Comair Y, Kotagal P, et al. Seizure outcome after epilepsy surgery in children and adolescents. *Ann Neurol* 1998;44(5):740-748. DOI:10.1002/ana.410440507
14. Spencer SS, Berg AT, Vickrey BG, et al. Predicting long-term seizure outcome after resective epilepsy surgery: The multicenter study. *Neurology* 2005;65:912-918. DOI:10.1212/01.wnl.0000176055.45774.71
15. Schwartz TH, Jeha L, Tanner A, Bingaman W, Sperling MR. Late seizures in patients initially seizure free after epilepsy surgery. *Epilepsia* 2006;47(3):567-573. DOI:10.1111/j.1528-1167.2006.00469.x
16. Paolicchi JM, Jayakar P, Dean P, et al. Predictors of outcome in pediatric epilepsy surgery. *Neurology* 2000;54(3):642-647. DOI:10.1212/WNL.54.3.642
17. Mathern GW, Giza CC, Yudovin S, et al. Postoperative seizure control and antiepileptic drug use in pediatric epilepsy surgery patients: The UCLA experience, 1986 - 1997. *Epilepsia* 1999;40(12):1740-1749. DOI:10.1111/j.1528-1157.1999.tb01592.x
18. Menon R, Rathore C, Sarma SP, Radhakrishnan K. Feasibility of antiepileptic drug withdrawal following extratemporal resective epilepsy surgery. *Neurology* 2012;79(8):770-776. DOI:10.1212/WNL.0b013e3182644f7d
19. Schmidt D, Baumgartner C, Löscher W. Seizure recurrence after planned discontinuation of antiepileptic drugs in seizure-free patients after epilepsy surgery: A review of current clinical experience. *Epilepsia* 2004;45(2):179-186. DOI:10.1111/j.0013-9580.2004.37803.x
20. Mani J, Gupta A, Mascha E, et al. Postoperative seizures after extratemporal resections and hemispherectomy in pediatric epilepsy. *Neurology* 2006;66(7):1038-1043. DOI:10.1212/01.wnl.0000204236.96232.1c