

SURGICAL TREATMENT IN REFRACTORY EPILEPSY

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INTRODUCTION

- ▶ The benefits and risks of epilepsy surgery are well described and the results are consistent over time and across regions worldwide.
- ▶ Nonetheless, the notion remains that epilepsy surgery is substantially underutilized despite the emergence of class I evidence [1] and widely endorsed Clinical Practice Guidelines (CPGs) [2].

I. Weibe S. NEJM 2001. 2. Engel J. Neurology 2003.

EPILEPSY SUREGTRY IS UNDER-UTILIZED

- ▶ Two recent studies in US concluded that despite an increase in hospitalizations for epilepsy and in the number of presurgical evaluations, the utilization of epilepsy surgery has not increased over time [1,2].
- ▶ Disparities in the use of epilepsy surgery has higher rates in white people and in those with private insurance.

1. Englot DJ. Neurology 2012. 2. Schiltz NK. Epilepsy Res 2013.

EPILEPSY SUREGTRY IS UNDER-UTILIZED

- ▶ Gaps in knowledge and understanding about epilepsy surgery exist among many healthcare professionals providing care to those with epilepsy, as demonstrated in two recent European surveys [1,2].

1. Kuhlten E. Seizure 2010. 2. Erba G. Epilepsia 2012.

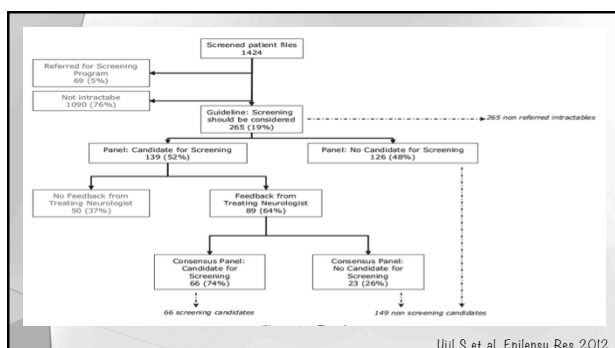


Table 2 Most Commonly mentioned reasons not to refer to presurgical work-up according to treating neurologist.

Reasons that were considered valid (25% of total)	
Type/classification of epilepsy	
Type of seizures	
Contra-indication for surgery	
Co-morbidity	
Low seizure frequency	
Low burden of seizures (judgement of patient)	
Patient does not want to undergo surgery	
Reasons that were considered invalid (75% of total)	
Low burden of seizures (judgement of neurologist)	
Psychogenic seizures apart from epileptic seizures	
Psychiatric co-morbidity	
Referral to screening program >5 yrs ago	

Ujil S et al. Epilepsy Res 2012.

SURGERY IS EFFECTIVE

- ▶ In the RCT of epilepsy surgery for temporal lobe epilepsy (TLE) of any cause, the ARR was 50% by intention to treat and 56% by efficacy analysis.
- ▶ This translates into an astounding number needed to treat (NNT) of only two. By comparison, the NNT to prevent stroke with carotid endarterectomy is about 10.

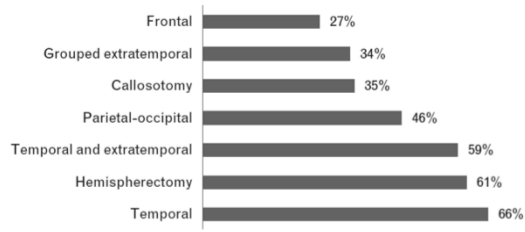
Weibe S. NEJM 2001.

SURGERY IS EFFECTIVE

- ▶ A systematic review of these studies demonstrated that after at least 5 years, the proportion of seizure-free patients was largely preserved over time [1].
- ▶ A recent systematic review explored the long-term net benefit of epilepsy surgery in cohort studies using nonrandomized medically treated controls and found an overall ARR of 4.2% [2].

1. Tellez-Zenteno JF. Brain 2005. 2. Schmidt D. Epilepsia 2009.

Percent seizure free



Tellez-Zenteno JF. Brain 2005.

SURGERY IS EFFECTIVE

- ▶ Overall, 55% of patients were seizure free at 5 years and 47% at 10 years, and of those who were seizure free in the first 2 years, 78% remained seizure free 10 years later.
- ▶ Of 66% of patients experiencing prolonged seizure remissions, over three quarters had sustained remission from the time of epilepsy surgery.

De Tisi J. Lancet 2011.

SURGERY IS COST-EFFECTIVE

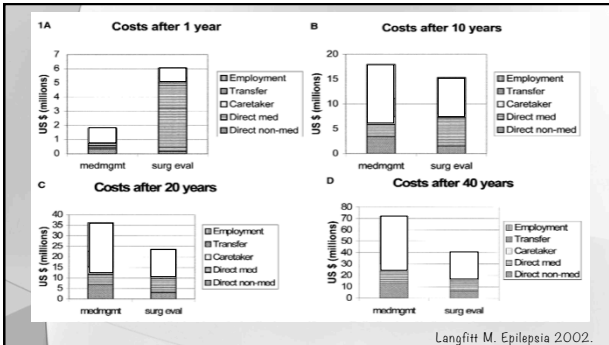
- ▶ Although the most refractory patients compose a minority (20-30%) of those with epilepsy, they account for a large share of the total costs of epilepsy [1].
- ▶ One study estimated that the 15% of patients who are most refractory account for \$ 50% of the total costs of the illness [2].

1. Sander JWAS. Epilepsy: a comprehensive textbook 1997. 2. Begley CE. Epilepsia 1994.

TABLE 1. Direct medical and nonmedical costs by seizure severity

	Number of seizures in past year			All patients (n = 785)
	0 (n = 377)	<1/mo (n = 204)	>1/mo (n = 204)	
Total health care costs	£61,235	£168,319	£311,118	£540,672
Cost per patient, total health care costs	162	825	1,525	689
Total health and non-health care direct costs	167,198	347,890	715,719	1,231,050
Cost per patient, total health and non-health care direct costs	443	1,705	3,508	1,568

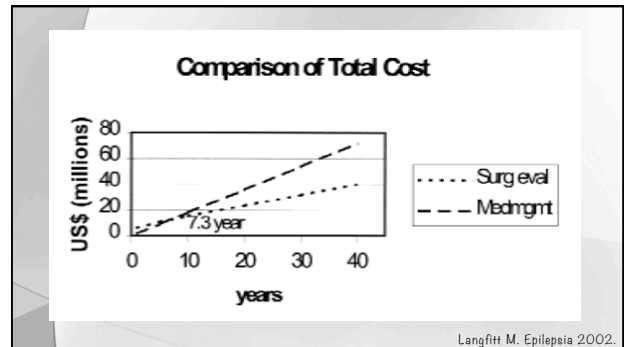
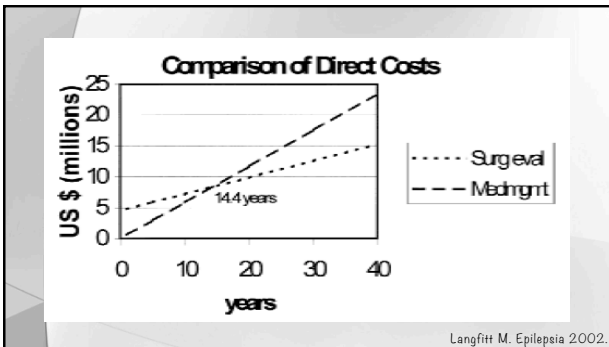
Jacoby A. Epilepsia 1998.



SURGERY IS COST-EFFECTIVE

- ▶ One year after, surgical patients who became seizure free after surgery had decreased caretaker costs.
- ▶ Transfer payments were decreased 2 years after, and employment gains reached a maximum at 5 years after surgery in seizure-free patients.

Langfitt M. Epilepsia 2002.



SURGERY IS COST-EFFECTIVE

- ▶ After an initial costly outlay, epilepsy surgery accrues savings over time and becomes cheaper than AEDs after 7 or 8 years of follow-up because of its ability to avert seizures and their associated costs [1-3].
- ▶ A recent pediatric study found epilepsy surgery to be incrementally cost-effective even at 1 year of follow-up [4].

1. Wiebe S. J Epilepsy 1996. 2. Pizat MC. Rev Neurol 2004.
3. Keene D. Childs Nerv Syst 1999. 4. Widjaja E. Epilepsy Res 2011.

SURGERY SAVES LIVES

- ▶ Refractory patients have a mortality rate about 5 times higher than the general population, but their risk of death is 2.4 times lower if they have epilepsy surgery and become seizure free [1].
- ▶ In a comprehensive decision analysis model of TLE, epilepsy surgery resulted in an average increase of 7.5 quality adjusted life years compared to AEDs [2].

1. Bell GS. JNMP 2010. 2. Choi H. JAMA 2008.

Table 2. Expected Outcomes of Decision Analysis

	Age at Surgery, y						
	15	25	35	45	55	65	75
Life Expectancy, Estimate (95% Confidence Interval), y							
Surgery	45.5 (41.9 to 56.4)	40.3 (34.2 to 47.3)	32.3 (27.0 to 36.5)	24.8 (20.2 to 29.9)	18.2 (14.4 to 22.4)	12.6 (9.6 to 15.9)	8.0 (5.9 to 10.5)
Medical management	43.9 (40.0 to 47.9)	35.6 (32.0 to 39.5)	27.3 (24.1 to 30.5)	19.4 (16.9 to 22.5)	13.2 (11.0 to 15.5)	8.0 (6.4 to 9.8)	4.4 (3.4 to 5.5)
Incremental benefit	4.6 (0.9 to 10.5)	4.7 (1.4 to 9.7)	5.0 (2.1 to 9.2)	5.2 (2.7 to 8.5)	5.0 (3.1 to 7.5)	4.6 (3.0 to 6.4)	3.6 (2.3 to 5.1)
Simulations preferring surgery, %	99.6	99.9	100	100	100	100	100
Quality-Adjusted Life Expectancy, Estimate (95% Confidence Interval), QALYs							
Surgery	42.1 (24.3 to 53.1)	35.2 (20.9 to 44.6)	28.4 (17.5 to 36.5)	22.1 (14.3 to 28.3)	16.4 (11.1 to 21.1)	11.5 (7.9 to 15.1)	7.4 (5.1 to 9.9)
Medical management	33.8 (12.4 to 43.9)	27.3 (10.2 to 35.8)	20.9 (7.9 to 27.7)	15.2 (5.9 to 20.3)	10.2 (4.0 to 13.8)	6.3 (2.5 to 8.7)	3.4 (1.5 to 4.9)
Incremental benefit	8.3 (-6.5 to 24.8)	7.9 (-3.3 to 21.0)	7.5 (-0.8 to 17.4)	6.9 (1.2 to 14.5)	6.2 (2.4 to 11.3)	5.2 (2.8 to 8.6)	4.0 (2.4 to 6.0)
Simulations preferring surgery, %	92.5	94.0	96.5	99.3	100	100	100

Abbreviation: QALY, quality-adjusted life year.

Choi H. JAMA 2008.

SURGERY IMPROVES QUALITY OF LIFE

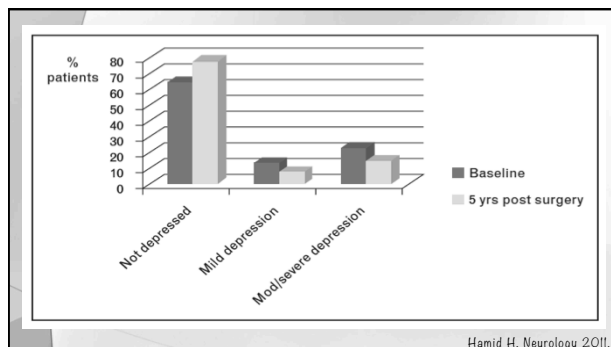
- ▶ About 90% of epilepsy surgery studies assessing quality of life (QOL) find that epilepsy surgery improves QOL.
- ▶ The improvement is prominently associated with good psychological function preoperatively and postoperatively and with seizure freedom postoperatively.

Seiam AH. Epilepsy Behav 2011.

SURGERY IMPROVES QUALITY OF LIFE

- ▶ Similarly, improvements occur after epilepsy surgery in patients' employment, relationships, independence, ability to drive, and overall lifestyle [1].
- ▶ Most studies also show improvement in psychiatric function [2].

I. Hamiuka L. Epilepsia 2011. 2. Maerodimitris S. Epilepsia 2011.



SURGERY IMPROVES QUALITY OF LIFE

- ▶ About 70% of patients are satisfied with epilepsy surgery outcomes, 64% consider it a success, and 87% would repeat epilepsy surgery if given the choice.

Maerodimitris S. Epilepsia 2011.

WHY IS EPILEPSY SURGERY NOT DONE

- ▶ Berg et al. have shown that sustained drug resistance and thus consideration of epilepsy surgery may not occur until much later after epilepsy onset.
- ▶ In their study, the average time from epilepsy onset to development of drug resistance was 9 years (range 0-46 years); moreover, 26% of patients experienced a remission prior to surgery and the remission lasted at least 5 years in nearly 10% of patients.

Berg AT. Neurology 2003.

WHY IS EPILEPSY SURGERY NOT DONE

- ▶ On the other hand, these data demonstrate that 74% of patients never experience a 1-year remission, and that in about 40% the latency to drug resistance was less than 8 years.
- ▶ Therefore, the question remains as to why patients who become drug resistant are not referred for presurgical evaluation in a timely manner.

Berg AT. Neurology 2003.

WHY IS EPILEPSY SURGERY NOT DONE

- ▶ In meta-analyses of epilepsy surgery, neurosurgical complications such as stroke, hemorrhage, and infection occur in about 5% of patients, and surgical mortality is rare [1].
- ▶ The major concern in TLE surgery is the risk of cognitive decline. A recent meta-analysis shows that reliable declines in verbal memory and naming function occur in about 40% of patients after dominant TLE surgery [2].

1. Tellez-Zenteno JF. Brain 2007. 2. Sherman EM. Epilepsia 2011.

WHY IS EPILEPSY SURGERY NOT DONE

- ▶ However, in a large prospective cohort study, QOL improved in patients who became seizure free after TLE surgery even if they had cognitive declines.
- ▶ QOL deteriorated most in patients who suffered cognitive decline and ongoing seizures after epilepsy surgery.

Langfitt JT. Neurology 2007.

WHY IS EPILEPSY SURGERY NOT DONE

- ▶ African Americans have lower rates of epilepsy surgery than non-African Americans [1].
- ▶ Clinician's knowledge and attitudes toward epilepsy surgery play a role in the decision to refer patients for epilepsy surgery and they vary in different cultures and contexts [2-3].

1. Burneo JG. Neurology 2005. 2. Kumlien E. Seizure 2010. 3. Hakimi AS. Epilepsy Behav 2008.

INDICATION FOR EPILEPSY SURGERY

- ▶ Terminology such as 'acceptable seizure control', 'adequate response' to treatment and 50% responder rates have been used over the years to describe 'good outcomes' when patients still have seizures [1].
- ▶ Even one seizure a year can cause injuries, poor psychosocial outcomes, and mortality. Auras can also have deleterious effects on QOL [1,2].

1. Gilliam FO. Epilepsy Behav 2011. 2. Vickrey BG. Epilepsia 1994.

INDICATION FOR EPILEPSY SURGERY

- ▶ In a recent study of diverse epilepsy surgery procedures in children less than 3 years old, 48% were seizure free and 38% experienced greater than 75% seizure reduction [1].
- ▶ Adults greater than 50 years old had comparable long-term results to those less than 50 years old, that is, 95.2 and 90.5% achieved Engel class I or II outcomes, respectively [2].

1. Dunkley C. Epilepsy Res 2011. 2. Murphy M. Epilepsia 2010.

INDICATION FOR EPILEPSY SURGERY

- ▶ In a recent study, 85% of patients with histologically confirmed cortical dysplasia had MRIs reported as normal when performed outside a major epilepsy center [1], but only 35% of these MRIs were still normal when performed at the epilepsy center.
- ▶ Although those with lesional epilepsy have better seizure outcomes (68% seizure free), many of those with 'nonlesional' epilepsy (43%) also achieve seizure freedom [2].

1. Salamon N. Neurology 2008. 2. Tellez-Zenteno JF. Epilepsy Res 2010.

INDICATION FOR EPILEPSY SURGERY

- ▶ Two recent studies confirmed the above findings. One study found that 40% of 38 patients with MRI-negative TLE who underwent surgery achieved an Engel I seizure outcome [1].
- ▶ Another study reported that 60% of TLE patients with normal MRI achieved an Engel I surgical outcome [2].

1. Immonen A. Epilepsia 2010. 2. Bell ML. Epilepsia 2009.

EPILEPSY SURGERY GUIDELINES

- ▶ ILAE guidelines recommend epilepsy surgery evaluation in child
 - ▶ With failure of 2 appropriate AEDs or disabling (including side effects) seizures.
 - ▶ With epilepsies that cannot be assigned to an electroclinical syndrome but with stereotyped, lateralized, or focal seizures (except for idiopathic partial epilepsy).
 - ▶ In whom the MRI reveals a lesion amenable to surgical removal.
 - ▶ With seizures, and those requiring hemispherectomies and multilobar resections.

Cross JH. Epilepsia 2006.

EPILEPSY SURGERY GUIDELINES

- ▶ The AAN has produced quality-of-care indicators for epilepsy, which will be used to determine pay-per-performance for primary care physicians and neurologists.
- ▶ Recommendation NO. 6 requires "All patients with a diagnosis of intractable epilepsy who were considered for referral for a neurologic evaluation of appropriateness for surgical therapy and the consideration was documented in the medical record within the past 3 years."

Fountain NB. Neurology 2011.

WHEN SHOULD PATIENTS BE REFERED

- ▶ If drug-resistant patients keep trying different AEDs year after year, about 20% eventually may achieve a 1-year remission period [1,2]. However, the great majority of these patients will relapse again [2].
- ▶ In a recent incident cohort of 128 children with DRE, 57% experienced at least one 12-month seizure remission period [49]. However, relapses occurred in 68% of these patients, and repeated relapses and remissions were common.

1. Luciano AL. Ann Neurol 2007. 2. Choi H. Epilepsia 2008.

WHEN SHOULD PATIENTS BE REFERED

- ▶ In a recent study of adults with DRE, the cumulative probability of entering a seizure remission period was 5% per year, but 71% eventually relapsed.

Callaghan B. Epilepsia 2011.

WHEN SHOULD PATIENTS BE REFERED

- ▶ In the Early Randomized Surgical Epilepsy Trial (ERSET) study, Engel et al. [28**] compared ATL resection with optimum medical therapy in patients with disabling seizures for 2 years or less.
- ▶ Although the trial was terminated after only 38 of the intended 200 patients were enrolled, surgery was significantly superior (73% seizure free) than medical therapy (0% seizure free) in the second postsurgical year ($P < 0.001$). Quality of life was also superior with surgery ($P = 0.01$).

Table 1. Who should be referred to a comprehensive epilepsy program for epilepsy surgery evaluation?

Indication	Comment
Any adult or child who meets the definition of DRE	Definition of DRE: Failure of adequate trials of two tolerated, appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom [37**]
Children or adults with complex syndromes or requiring complex surgeries	Example of complex syndromes: Rasmussen's encephalitis, tuberous sclerosis, Sturge-Weber syndrome, Landau-Kleffner syndrome, polymicrogyria, hypothalamic hamartoma, Dravet syndrome, Lennox-Gastaut syndrome, West syndrome, Ohtahara syndrome, infantile spasms, epilepsia partialis continua Example of complex surgeries: hemispherectomies, multilobar resections, and palliative procedures
Children or adults with epilepsies that cannot be clearly assigned to a known electroclinical syndrome but with stereotyped or lateralized seizures or focal findings	See the ILAE proposed new organization of seizures and epilepsies [44]
Children with an MRI lesion amenable to surgical removal regardless of seizure status	Recommended by the Subcommission for Pediatric Epilepsy Surgery because these children are more likely to relapse, and at high risk of developing epileptic encephalopathy, especially at a younger age [40]
Any child less than 3 years old with epilepsy	

Weibe S & Jette N. *Curr Opin Neurol* 2012.

Table 1. Questions used in online tool to determine candidacy for an epilepsy surgery evaluation

Question	Possible answers
1. What type of seizure does your patient have?	1. Simple partial seizure 2. Complex partial seizures or secondary generalized tonic-clonic seizures
2. How long has your patient had epilepsy?	1. Less than 1 year 2. More than 1 year
3. How often does your patient have seizures?	1. Seizure free 2. Less than one seizure per year 3. One to twelve seizures per year 4. One seizure per month or more
4. How severe are the seizures when they occur?	1. Non-disabling type of seizures 2. Disabling type of seizure
5. How many AEDs has your patient tried?	1. 0 2. 1 3. 2 4. 3 or more
6. Does your patient have side-effects with their current AED?	1. No 2. Yes
7. What investigations were done?	1. None 2. EEG only 3. MRI only 4. EEG and MRI
8. What were the results of the investigations?	1. EEG and MRI both normal 2. EEG normal, MRI abnormal 3. EEG abnormal, MRI normal 4. EEG and MRI both abnormal

www.EpilepsyCases.com

Jette N, Quan H, Tellez-Zenteno JF, et al. *Neurology* 2012.

REFERENCE

- ▶ Uijt SG. Epilepsy surgery can help many more adult patients with intractable seizures. *Epilepsy Res.* 2012.
- ▶ Platt M. A Comparison of surgical and medical costs for refractory epilepsy. *Epilepsia* 2002.
- ▶ Koubeissi M. Epilepsy surgery: A broken bridge between utility and utilization. *Epilepsy Cur.* 2013.
- ▶ Jette N. Update on the surgical treatment of epilepsy. *Curr Opin Neurol* 2013.
- ▶ Wiebe S. Epilepsy surgery utilization: who, when, where and why? *Curr Opin Neurol* 2012.