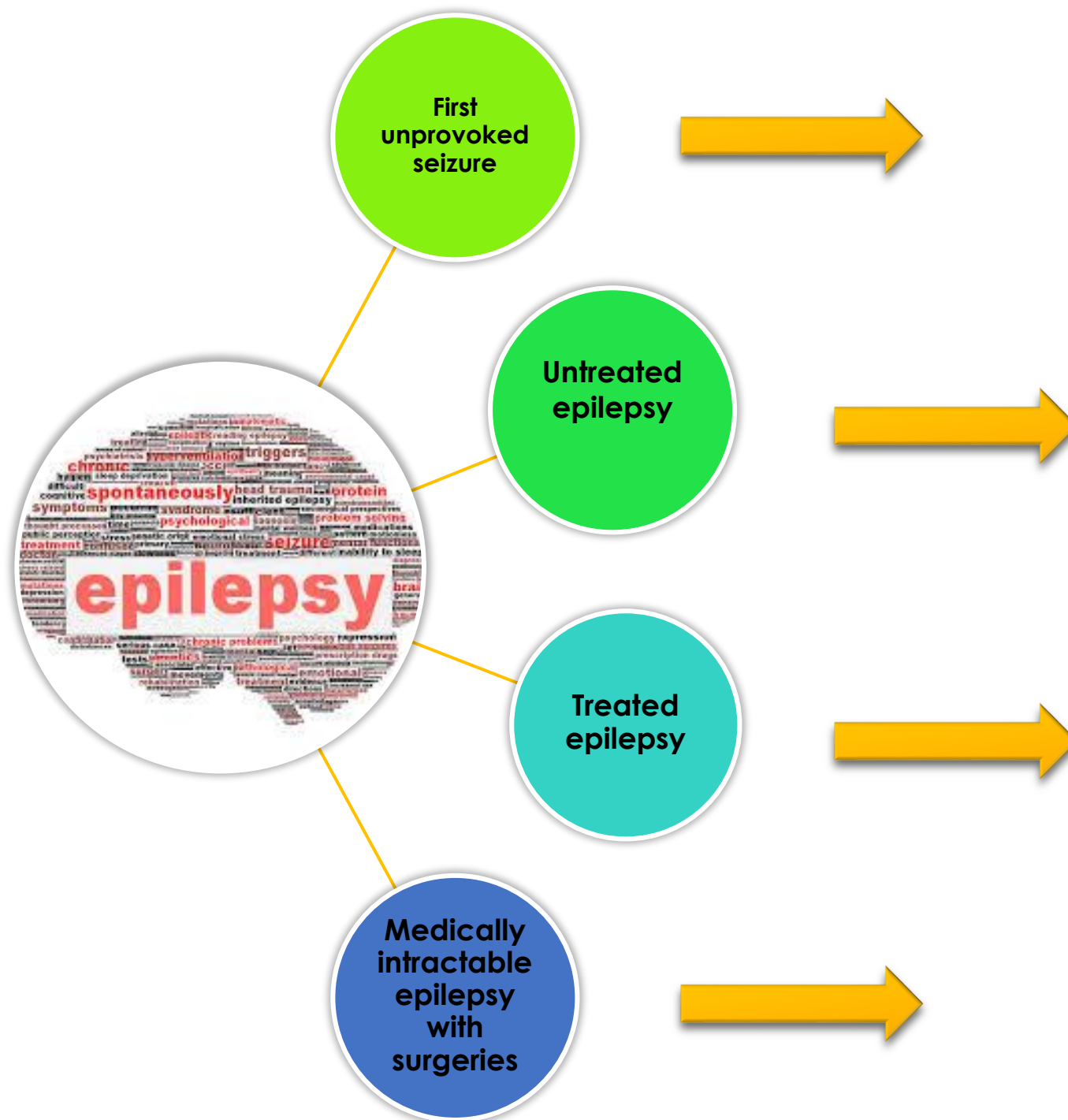



# What do we know about prognosis and natural course of epilepsies ?

---

**Dr. Chusak Limotai, MD., M.Sc., CSCN (C)**  
**Chulalongkorn Comprehensive Epilepsy Center of Excellence (CCEC)**  
**The Thai Red Cross Society**



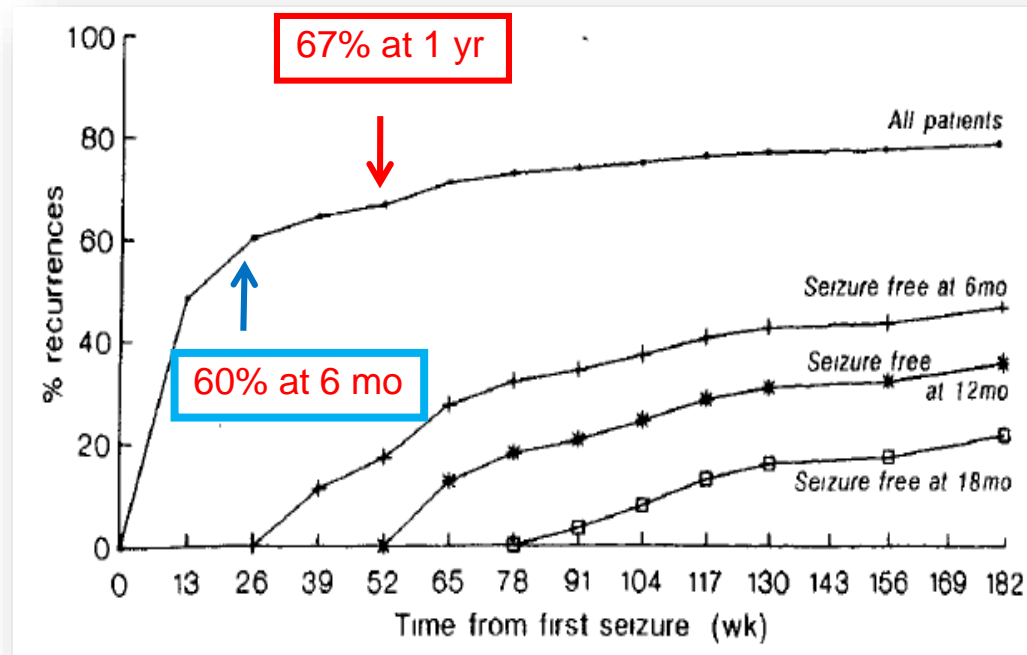


# **Natural course and prognosis of first unprovoked seizure**

# Early prognosis:

## Risk of recurrence after first unprovoked seizure

- ✓ Pooled estimate of 2 year recurrence risk = **42% (30-50%)**



78% at 3 yrs

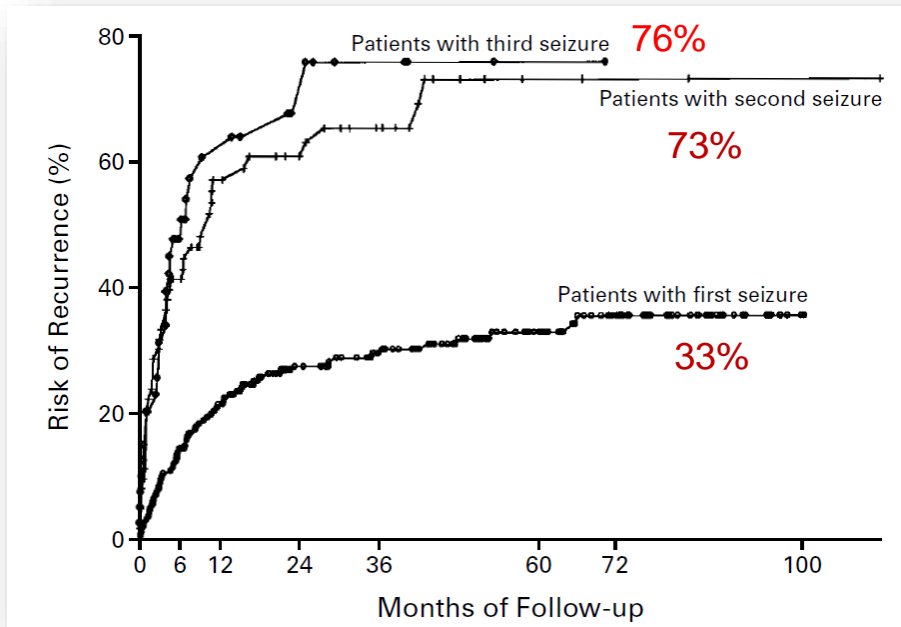
44 % at 3yrs

32 % at 3yrs

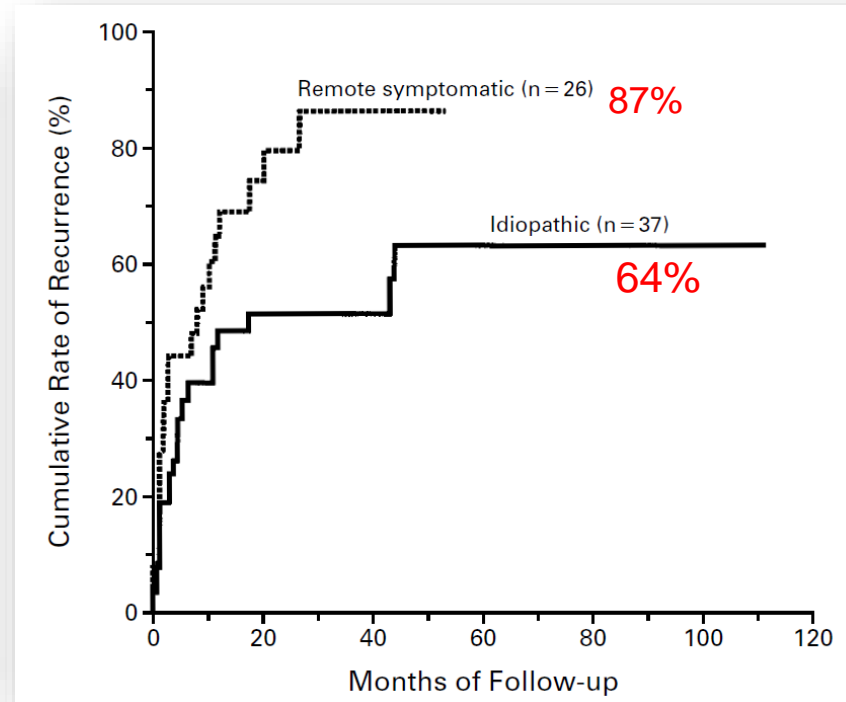
17 % at 3yrs

# Risk of recurrence

## After first, second and third seizure



## Etiology



# What are the predictors of recurrence?

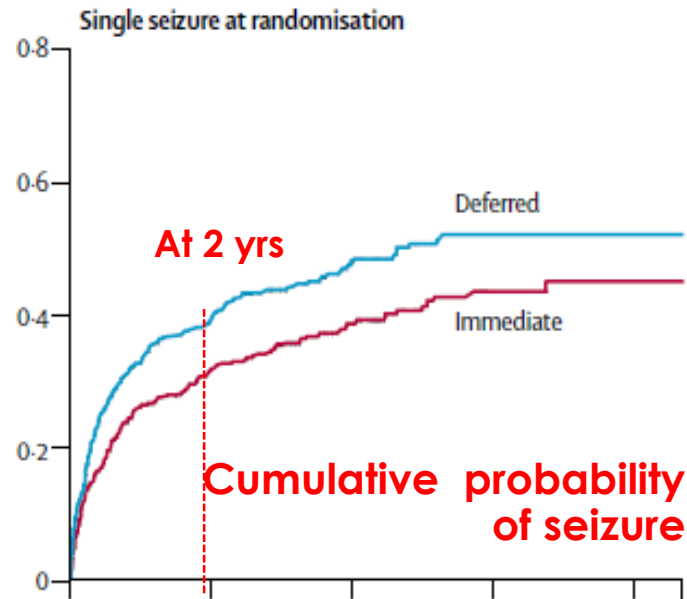
**Abnormal  
neurological status  
and abnormal EEG**

| Predictor                                | Pooled RR of recurrence | Pooled risk of 2 year recurrence (%) |
|--|-------------------------|--------------------------------------|
| Abnormal neurological status             | 1.8                     | 57                                   |
| <u>Normal EEG</u>                        |                         | 27                                   |
| <u>Epileptiform abnormalities in EEG</u> | 2.0                     | 58                                   |
| Non-epileptiform abnormalities in EEG    | 1.3                     | 37                                   |
| Aetiology and EEG combined               |                         |                                      |
| Idiopathic + normal EEG                  |                         | 24                                   |
| Idiopathic + abnormal EEG                | 1.9                     | 48                                   |
| Remote symptomatic + normal EEG          |                         | 48                                   |
| Remote symptomatic + abnormal EEG        | 1.4                     | 65                                   |

EEG, electroencephalogram; RR, relative risk.

# Immediate vs deferred treatment after a first unprovoked seizure

Marson A et.al The Lancet 2005

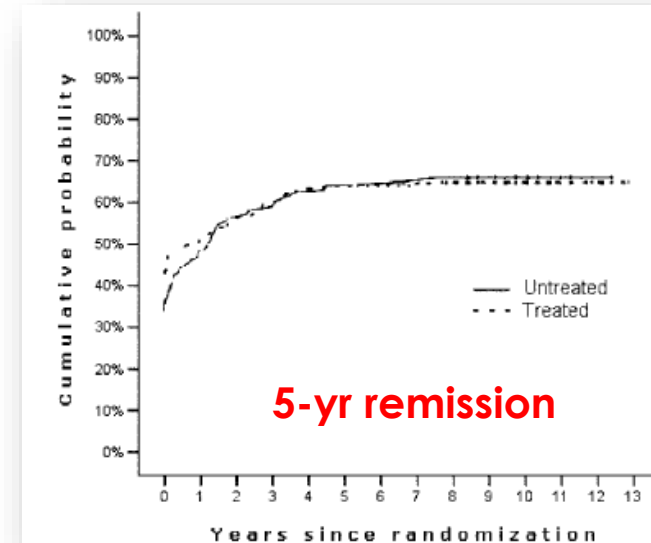
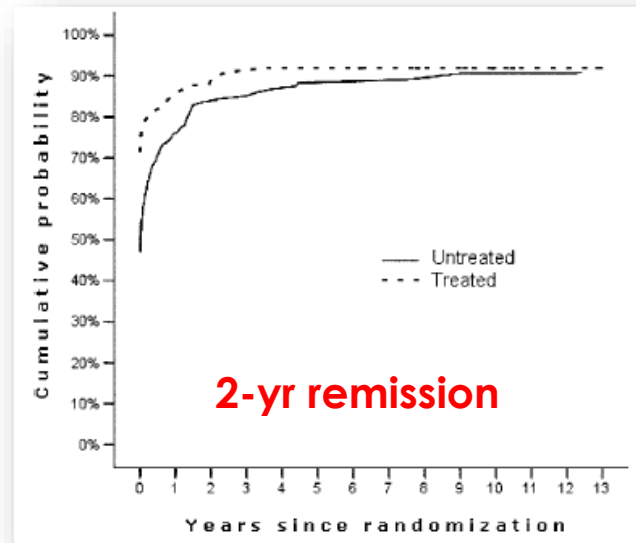


MESS studies

- 2 yr-remission: 69% vs 61%
    - At 3 yrs: 1-3 yrs sz remission: 74% vs 71%
    - At 5 yrs: 3-5 yr sz remission: 76% vs 77%
- “Immediate antiepileptic drug treatment reduces the occurrence of seizures in the next 1–2 years, but does not affect long-term remission in individuals with single or infrequent seizures”**

# Immediate vs deferred treatment after a first unprovoked seizure

## FIR.S.T. (First Seizure Trial) studies



- Treatment of the first seizure increased the probability of a 2-year remission in the first 3 years; however, the difference disappeared after a longer period of follow-up

(only patients with GTCs were included)



# Prediction of risk of seizure recurrence

| Prognostic Index   |             |
|--|-------------|
| Starting value   |             |
| One seizure prior to presentation  | 0           |
| Two or three seizures prior to presentation  | 1           |
| Four or more seizures prior to presentation  | 2           |
| Add if present   |             |
| Neurological disorder or deficit, learning disability, or developmental delay                                | 1           |
| Abnormal EEG   | 1           |
| Risk classification group for seizure recurrence*  | Final score |
| Low risk   | 0           |
| Medium risk  | 1           |
| High risk  | 2-4         |
| *See table 3 for probabilities of no seizure recurrence at specific time points for each of these subgroups. |             |
| Table 4: Prognostic index, with integer values   |             |

**MESS studies**

**“There is little benefit to immediate treatment in patients at low risk of seizure recurrence, but potentially worthwhile benefits are seen in those at medium and high risk”**

*Kim LG et.al The Lancet 2006*



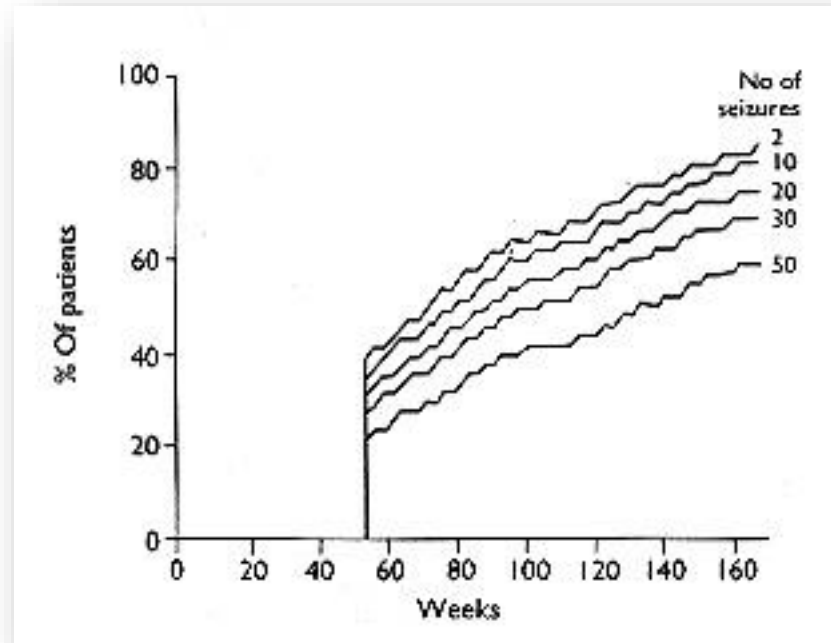
# **Natural course and prognosis of untreated epilepsies**

# Introduction

- **The course of disorders from onset to resolution, without interventions (Last, 1988)**
- **Evidence-based treatments with proven efficacy alter the natural course of disorders**
- **Prospective studies in untreated patients are thus not possible.**

# Effect of duration and number of seizure prior to treatment

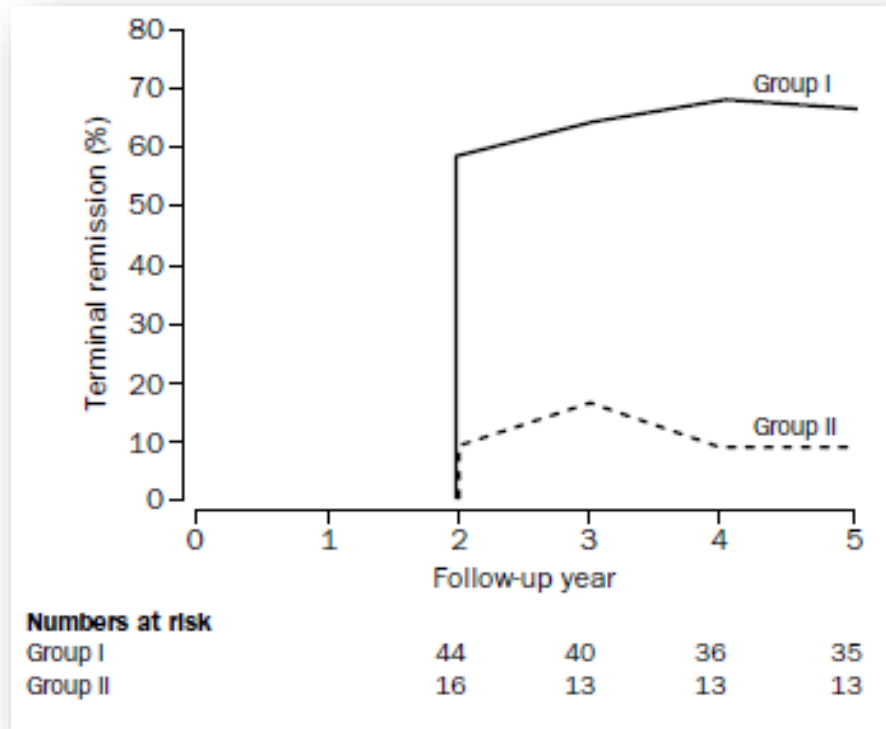
- Gower's observation and Reynolds EH studies pointed out that the longer the history of epilepsy the worse the longer term prognosis



**241 adults with newly diagnosed epilepsy treated with one drug**

Gowers WR 1881  
Reynolds EH; BMJ 1995  
Reynolds EH et.al; Epilepsia 1989

# Effect of number of seizure prior to treatment



**135 adult patients with partial seizure or GTCs**

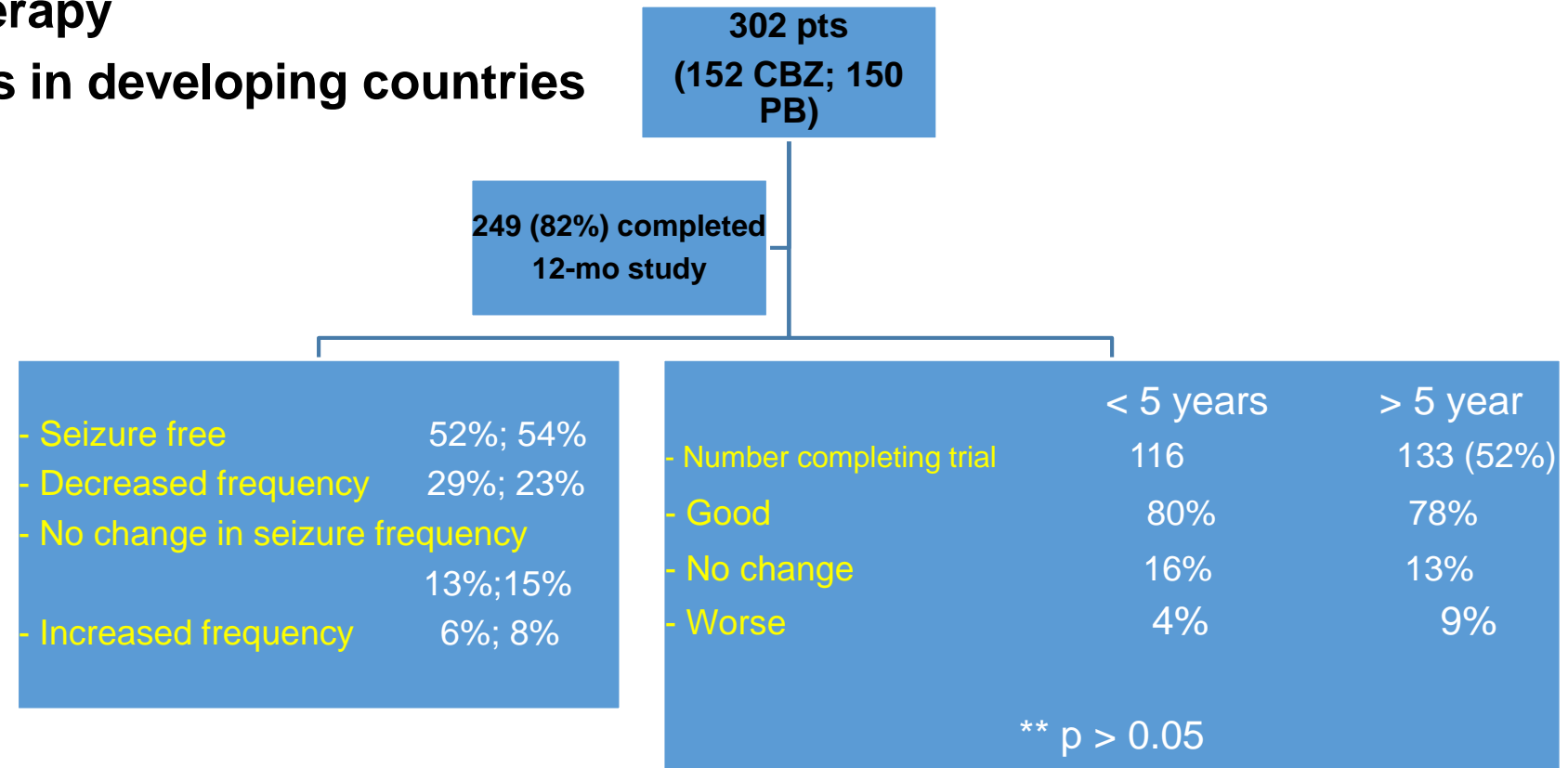
- Treated with either PB or PHT
- Primary outcome: 2-year seizure freedom

**Group I: good compliance coupled with lifetime total of  $\leq 30$  GTCs**

**Group II: poor compliance and lifetime total  $\geq 30$  GTCs**

# The effects of AEDs on long-lasting untreated epilepsy

- A study in Kenya (Lancet, 1991) : a finding that does not support the suggestion that the disorder becomes intractable if not treated early.
- Neither length of history of epilepsy nor number of seizures before treatment influenced effect of therapy
- Similar to other studies in developing countries (Malawi and Ecuador)



*Feksi AT et.al; Lancet 1991*  
*Watts AE; Br Med J 1989*  
*Placencia et.al; JNNP 1994*



# **Natural course and prognosis of treated epilepsies**

# “2001”

**TABLE 2. SUCCESS OF ANTIEPILEPTIC-DRUG REGIMENS IN 470 PATIENTS WITH PREVIOUSLY UNTREATED EPILEPSY.**

| VARIABLE   | No. (%)  |
|--|----------|
| Response to first drug                                     | 222 (47) |
| Seizure-free during continued therapy with first drug      | 207 (44) |
| Remained seizure-free after discontinuation of first drug  | 15 (3)   |
| Response to second drug                                    | 61 (13)  |
| Seizure-free during monotherapy with second drug           | 41 (9)   |
| Remained seizure-free after discontinuation of second drug | 20 (4)   |
| Response to third drug or multiple drugs                   | 18 (4)   |
| Seizure-free during monotherapy with third drug            | 6 (1)    |
| Seizure-free during therapy with two drugs                 | 12 (3)   |
| Total  | 301 (64) |

- 470 patients with newly-diagnosed epilepsy
- Seizure-free for at least 1 year
  - 1<sup>st</sup> drug: 47%
  - 2<sup>nd</sup> drug mono: 13%
  - 3<sup>rd</sup> drug mono: 1%
  - Two drugs: 3%

**Medically controlled: 64%**  
**Medically refractory: 36%**

## Effectiveness of AEDs



# “2012”

| Drug regimens | No. of patients | Seizure-free on monotherapy | Seizure-free on combination | Total no. seizure-free | % of cohort seizure-free | % Seizure-free on regimen |
|---------------|-----------------|-----------------------------|-----------------------------|------------------------|--------------------------|---------------------------|
| First         | 1,098           | 543                         | 0                           | 543                    | 49.5                     | 49.5                      |
| Second        | 398             | 101                         | 45                          | 146                    | 13.3                     | 36.7                      |
| Third         | 168             | 26                          | 15                          | 41                     | 3.7                      | 24.4                      |
| Fourth        | 68              | 6                           | 5                           | 11                     | 1.0                      | 16.2                      |
| Fifth         | 32              | 1                           | 3                           | 4                      | 0.4                      | 12.5                      |
| Sixth         | 16              | 1                           | 1                           | 2                      | 0.2                      | 12.5                      |
| Seventh       | 9               | 1                           | 1                           | 2                      | 0.2                      | 22.2                      |
| Eighth        | 3               | 0                           | 0                           | 0                      | 0.0                      | 0.0                       |
| Ninth         | 2               | 0                           | 0                           | 0                      | 0.0                      | 0.0                       |

**Medically controlled: 68%**

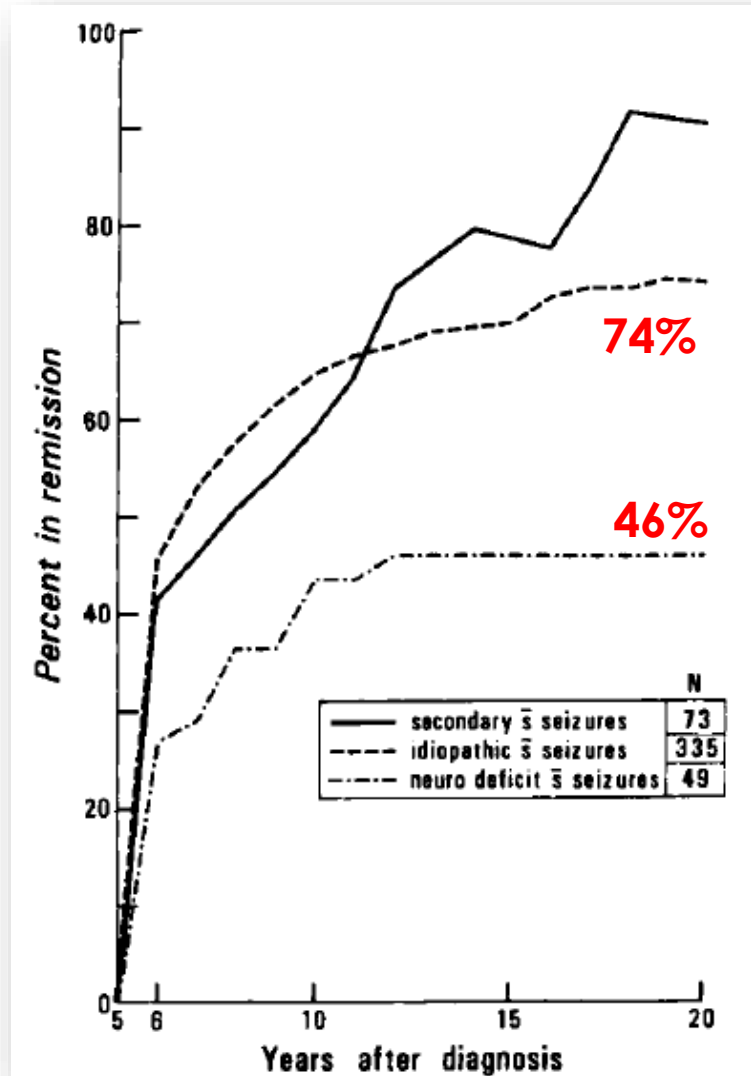
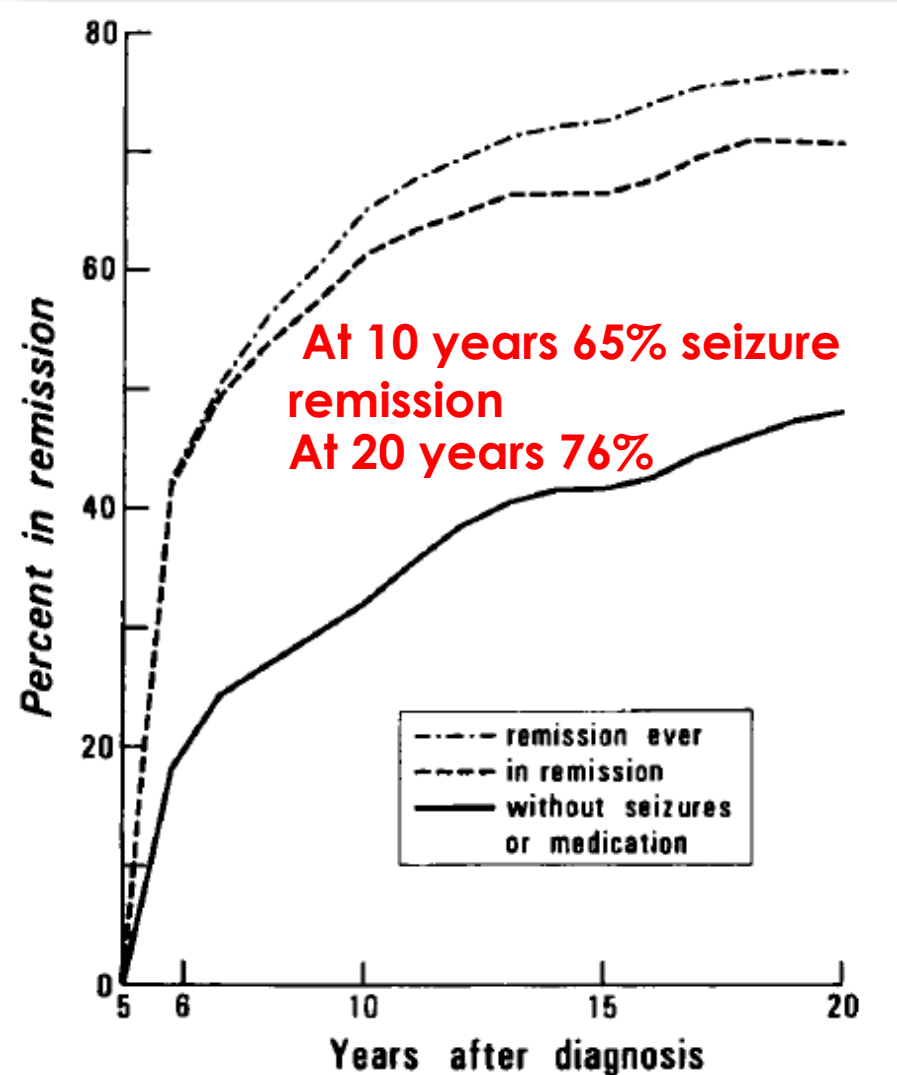
**Medically refractory: 32%**

- Despite the introduction of more than **15 new AEDs** (since 1985), there is limited evidence endorsing improved outcomes in the common adult epilepsies **over the past 30 years**
- Based on two large studies by the same group, there has been **slightly increased rate of seizure freedom** from **64% to 68%**

# Late prognosis

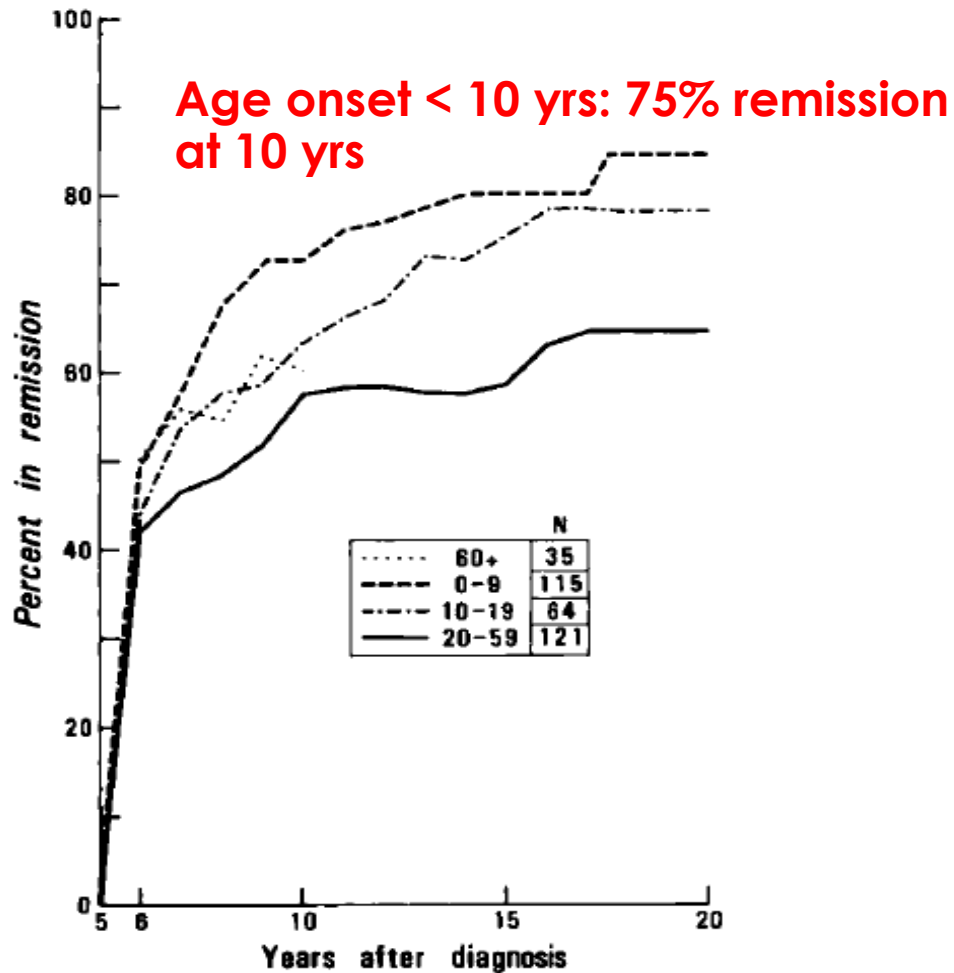
- **Based on 3 longitudinal community-based studies with long-term follow up**
  - **Mayo Clinic Record linkage study (US)**
  - **Tonbridge study (UK)**
  - **Turku study (Finland) (childhood-onset epilepsy)**

# Mayo clinic study (20 years follow up)

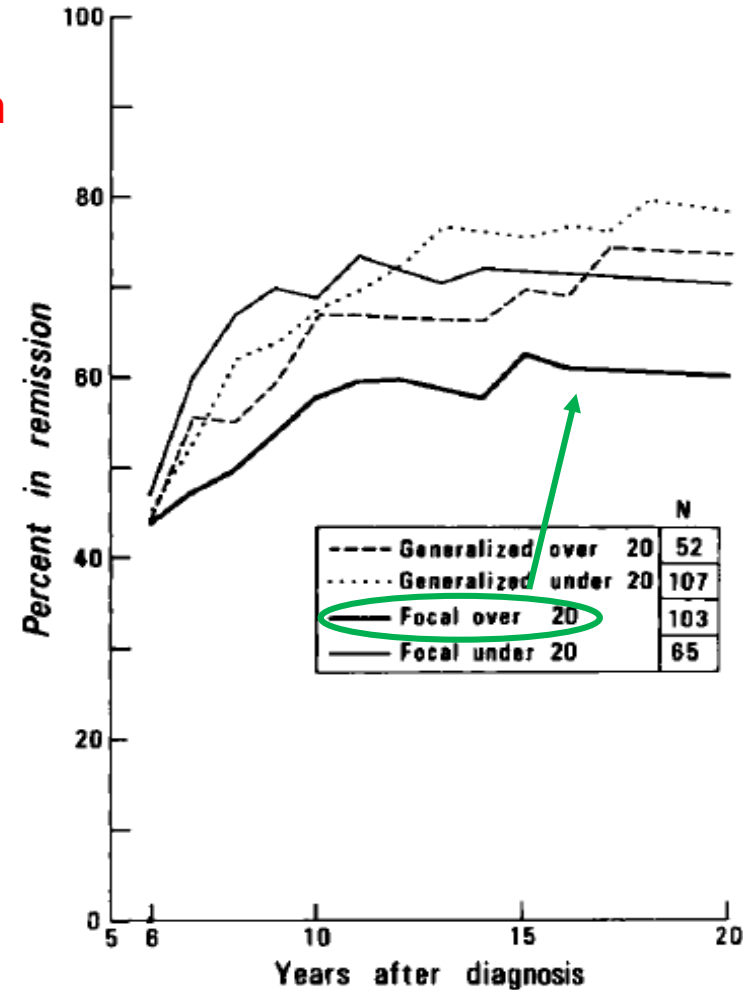


- 475 pts followed at least 5 yrs  
- 141 pts > 20 yrs

# Mayo clinic study

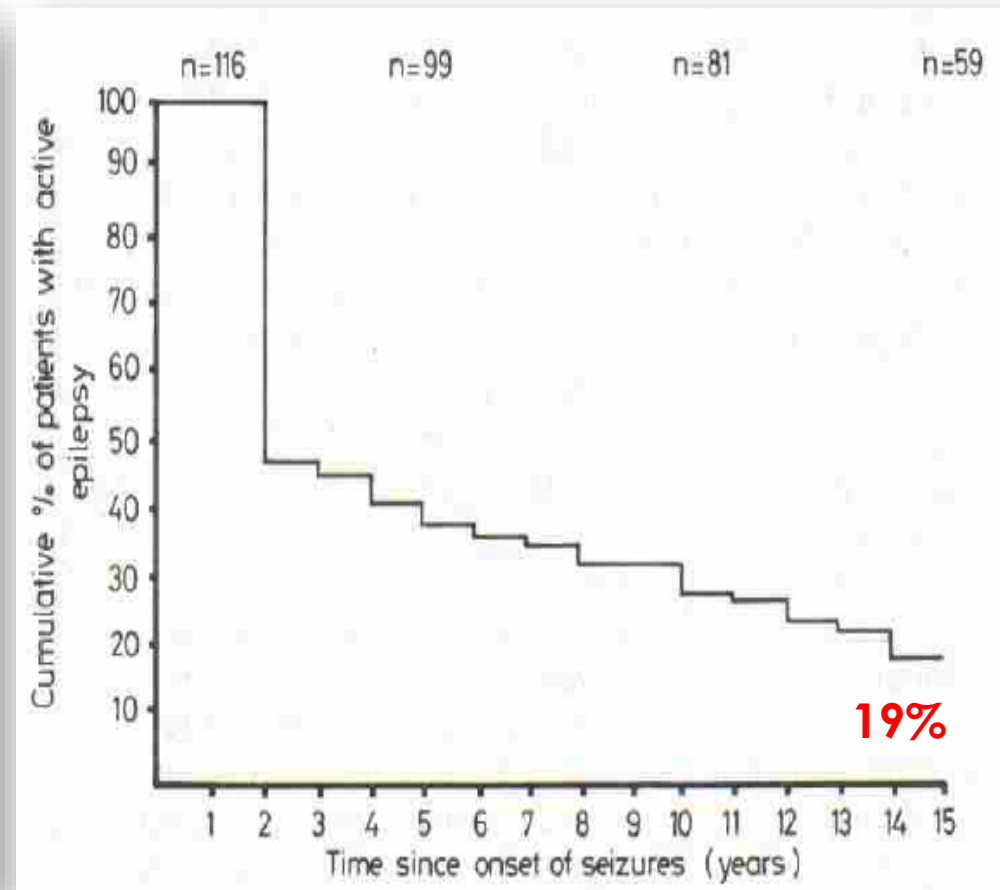
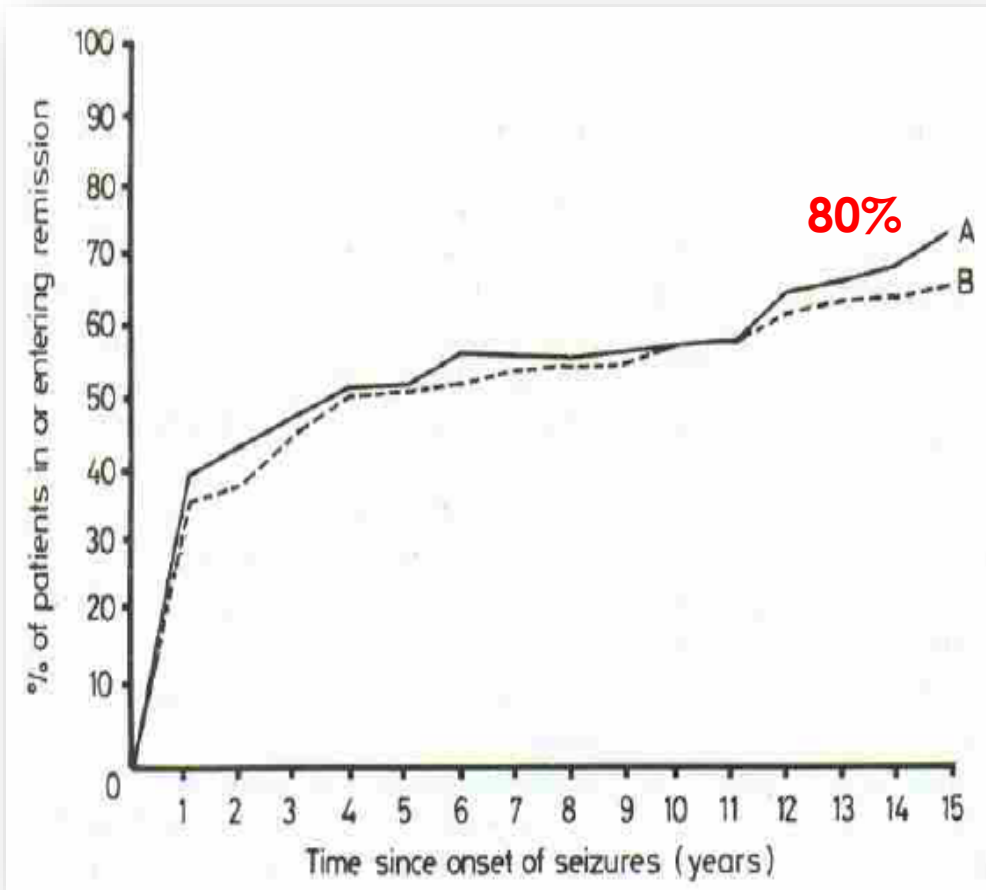


Higher remission: generalized-onset seizure diagnosed < 10 yrs



Lower remission: CPS with adult onset

# Tonbridge study (15 years follow up)

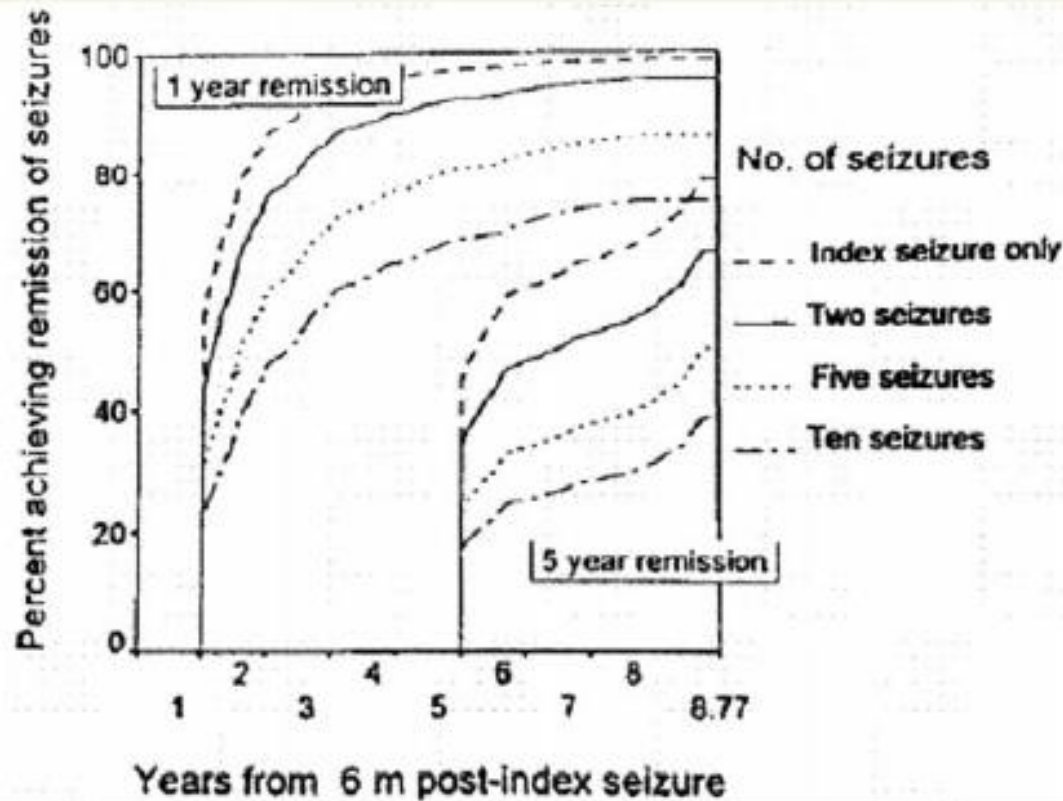


**About one fifth (20%) of the patients continued to have seizure (chronic epilepsy)**

# Tonbridge study

- At 5 years after the first seizure
  - of those whose epilepsy was still active, only 21% achieved subsequent terminal remission as compared with 96% of those who were already in remission

**“ the longer seizure continues to occur, the lower the probability for subsequent remission”**



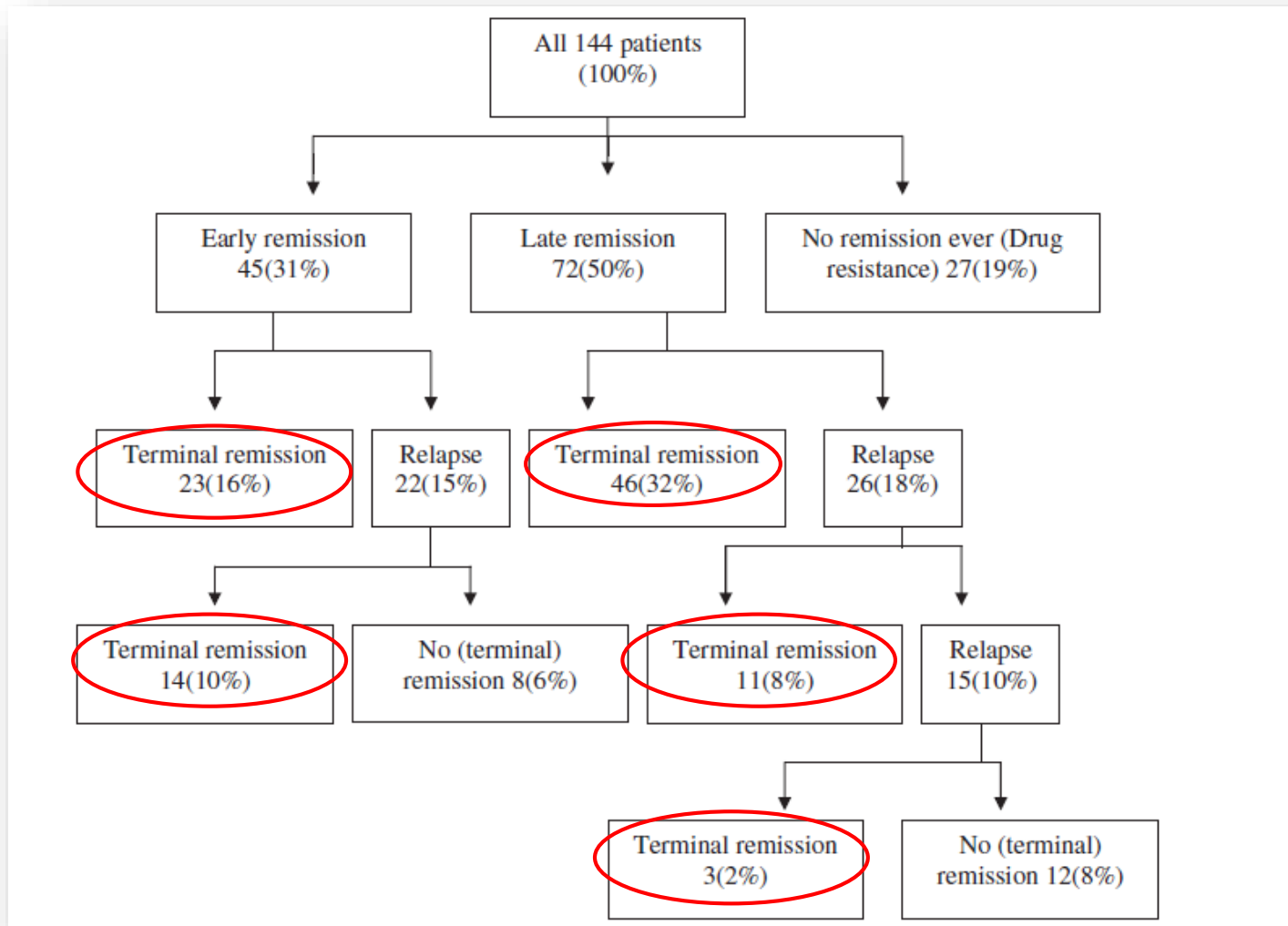
**Figure 2** NGPSE: the influence of seizure density on long-term remission. The percentage of patients achieving remission in those who had experienced one (dashed line), two (solid line), five (dotted line), or 10 (dashed and dotted line) seizures in the period from the index seizure to 6 months.

**The more number of seizure in the 6 months after the first seizure, the lesser is the chance of long-term remission**



# Turku study (37 years follow up)

- Seizure before the age of 16 years



- 67% achieved terminal remission (5-year seizure freedom at the end of follow up)
- 19% drug resistant
- 19% entered terminal remission after a relapse

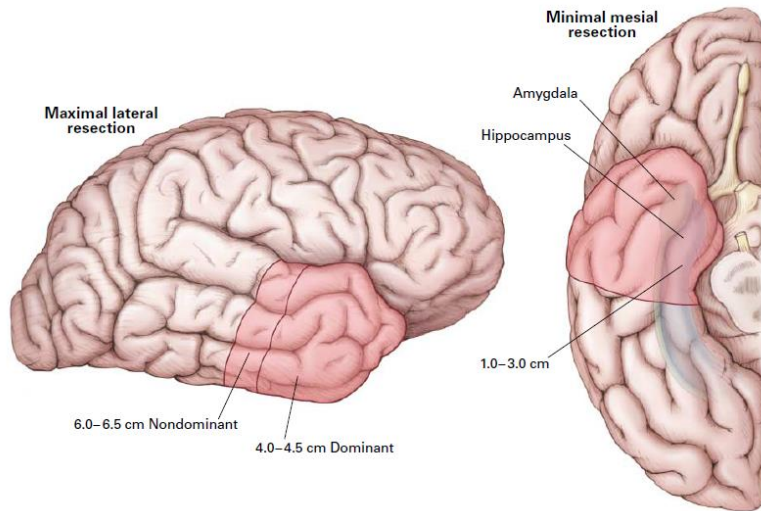
# Conclusion

- **2/3 of the patients (58-65%)** achieved 5-year cumulative terminal remission at 7-10 years follow up
- **3/4 of the patients (67-78%)** with childhood-onset epilepsy achieved 3-5 year remission at 12-37 years follow up
- **Neurological deficits, age onset, seizure type, number of early seizure influence on long-term remission rate**

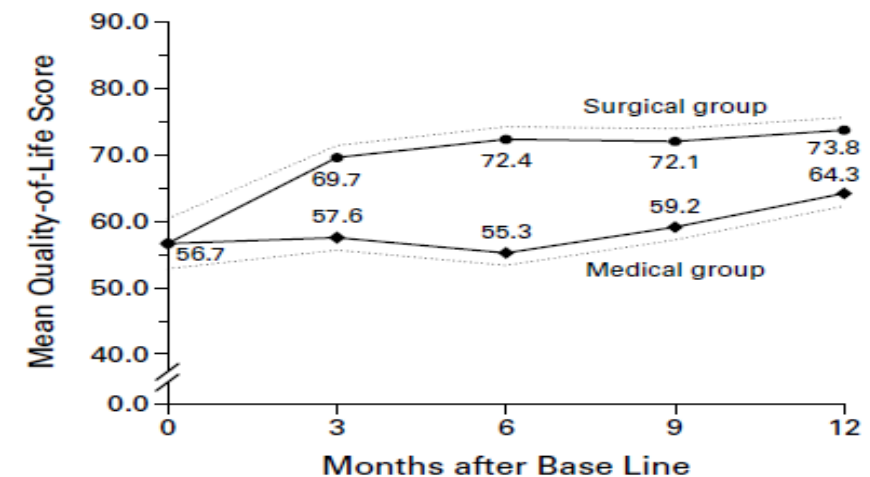
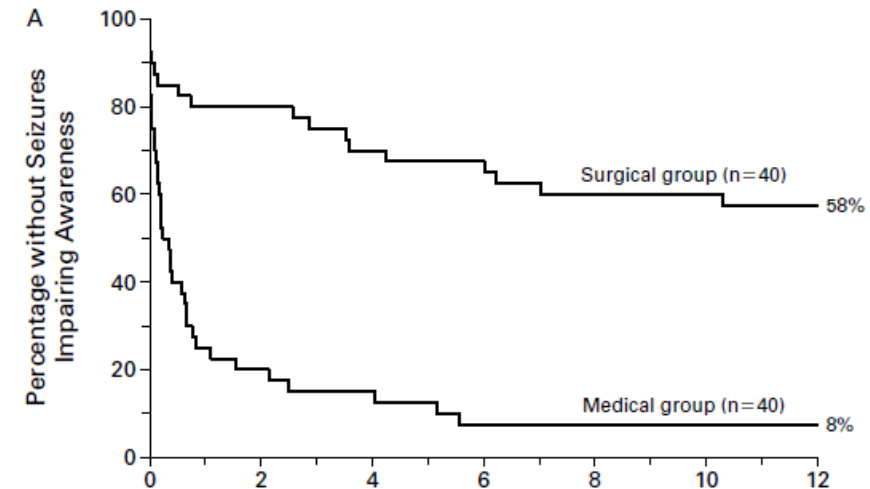


# **Natural course and prognosis of medically intractable epilepsy with surgeries**

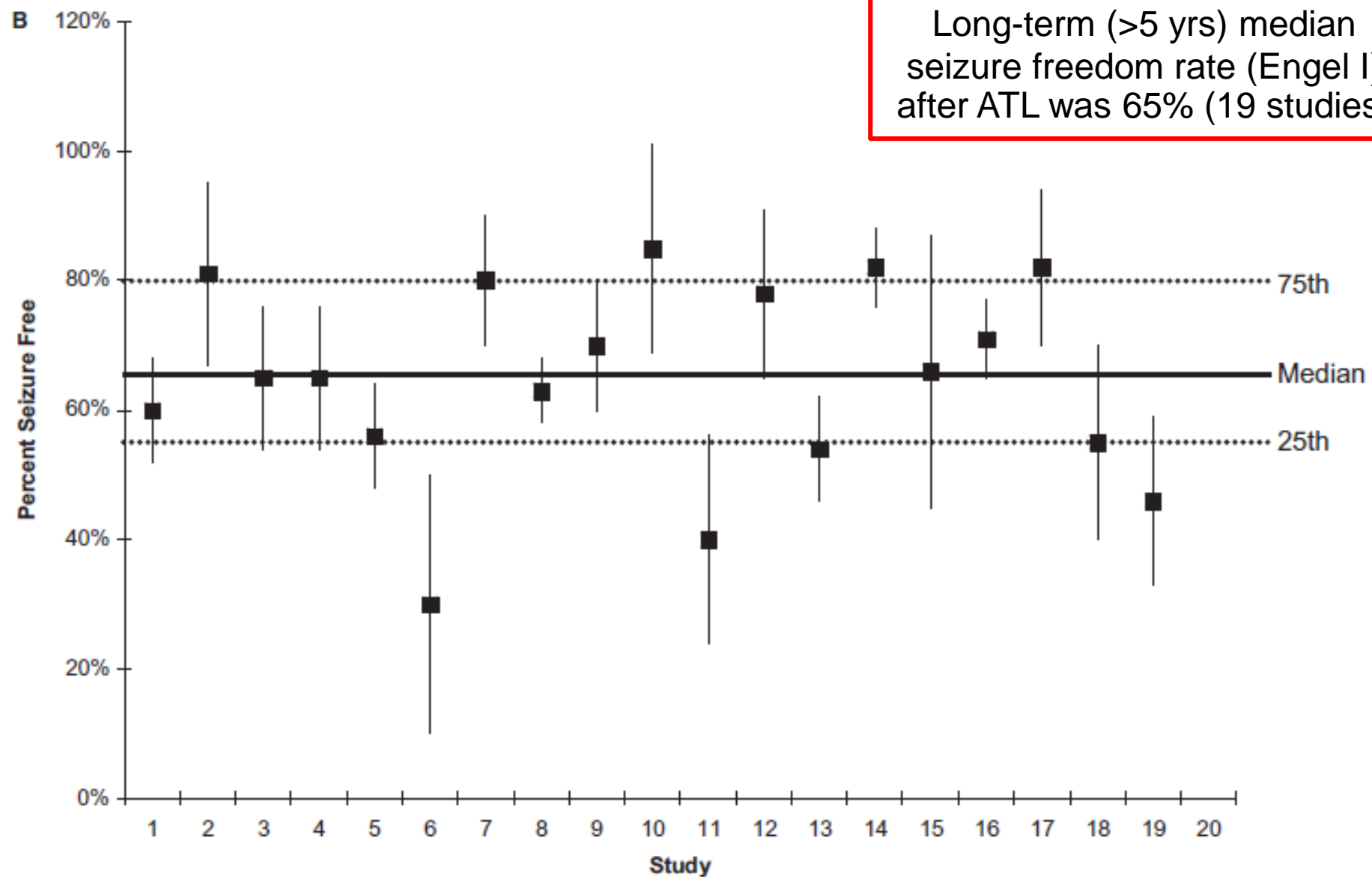
# RCT of surgery for temporal lobe surgery

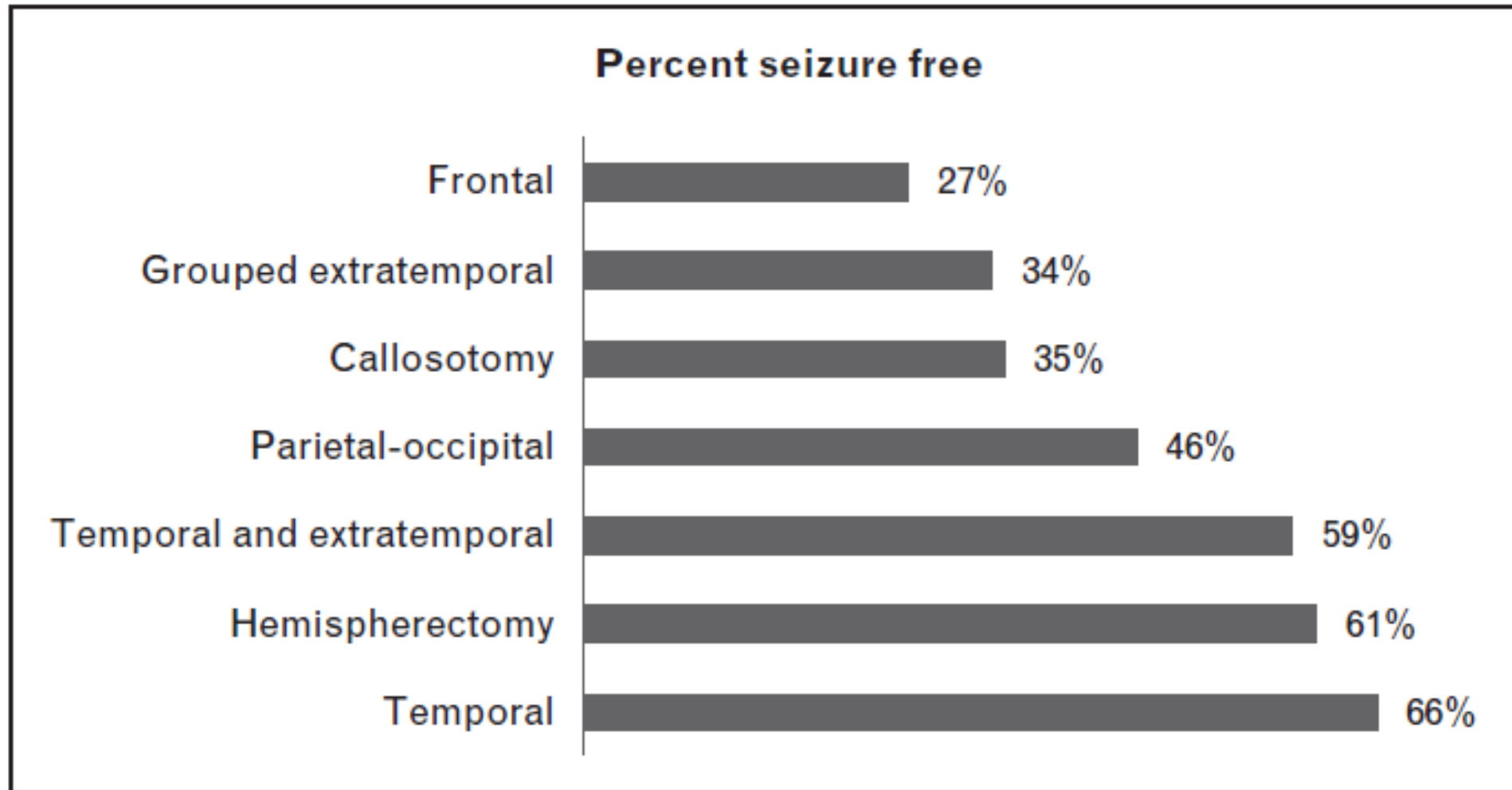


**The patients in the surgical group had fewer seizures impairing awareness and a significantly better quality of life ( $P < 0.001$  for both comparisons) than the patients in the medical group**



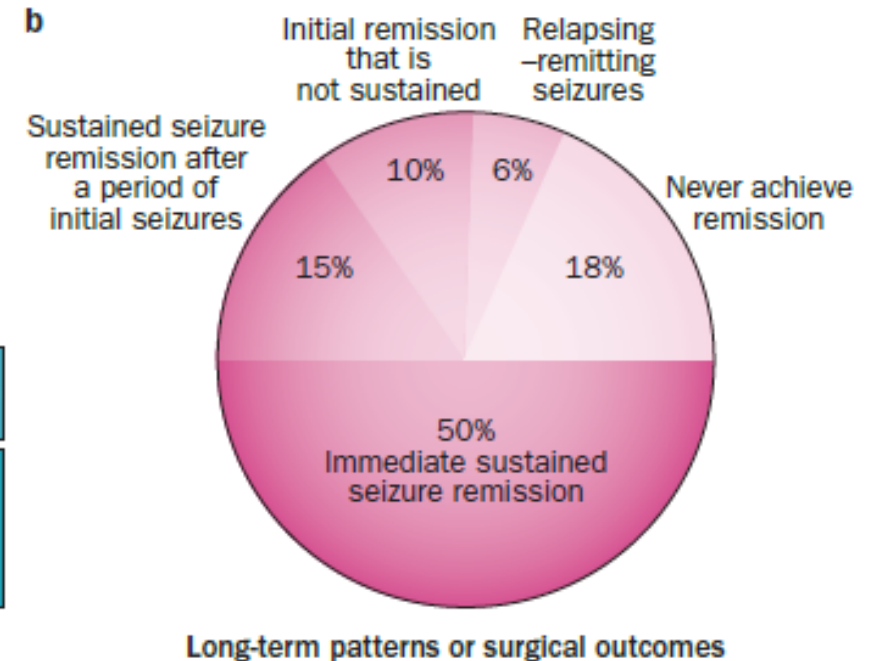
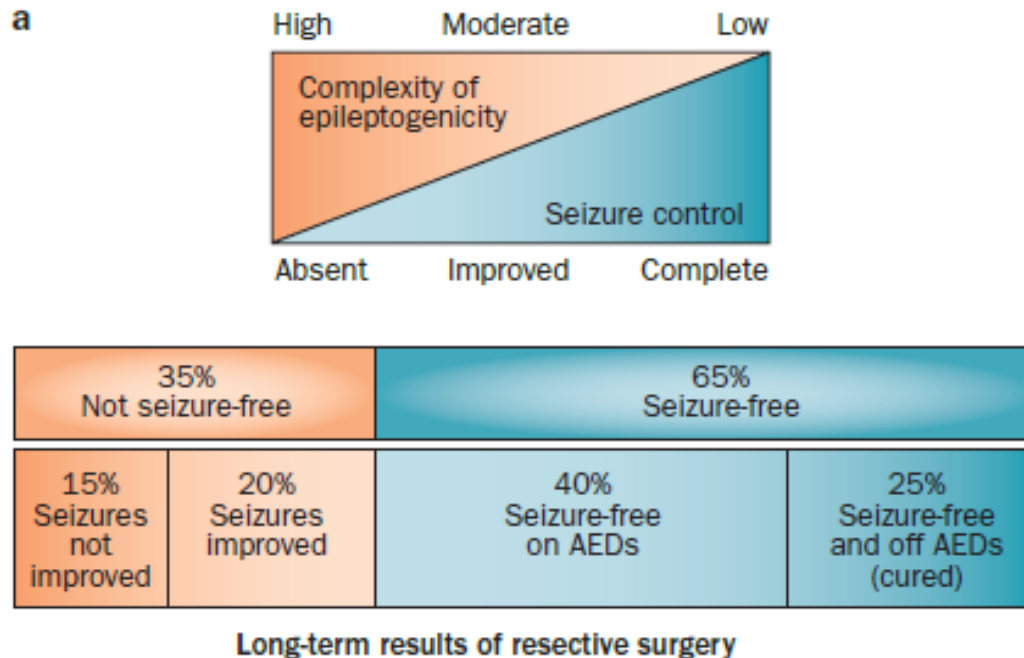
Wiebe S et.al; NEJM 2001





*Tellez-Zenteno JF et.al; Brain 2005  
Weibe S and Jette N; Curr Opin Neurol 2012*

# The outcome of surgical treatment in patients with epilepsy



# Referred cases at CCEC

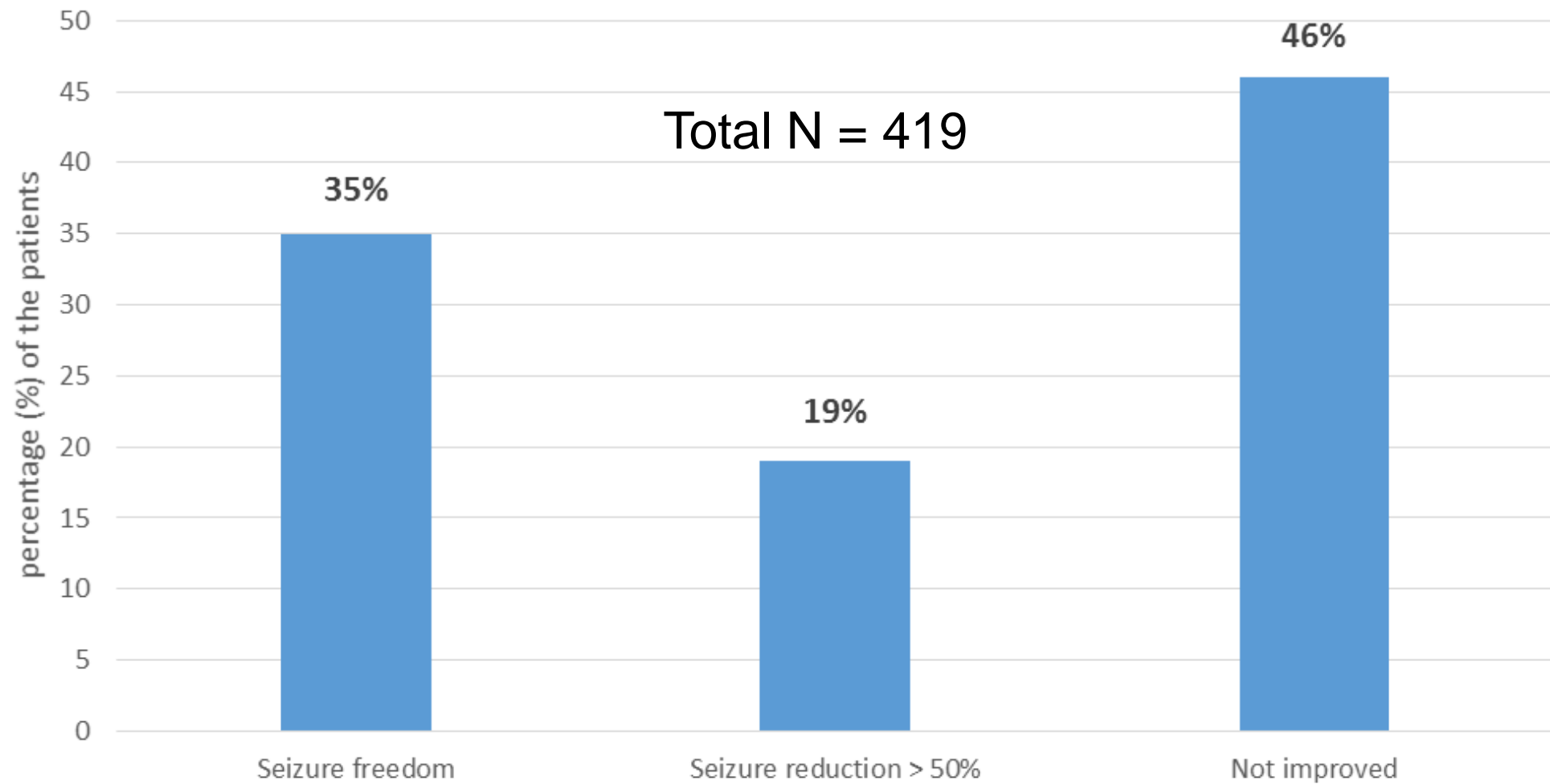
**Continuing seizures due to inadequate AEDs adjustment**

**Medically intractable TLE**

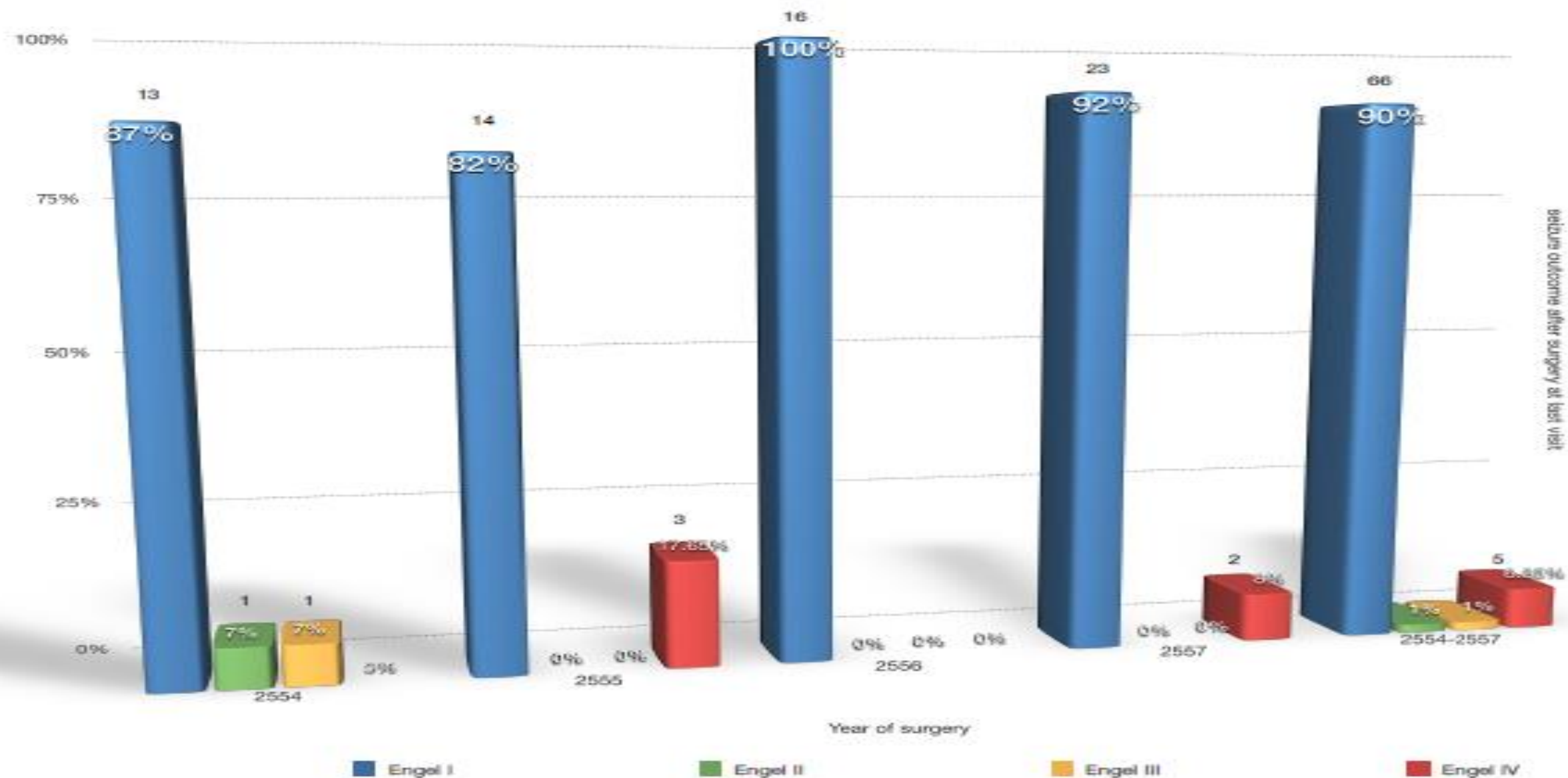
**Difficult surgical cases requiring extensive investigations**



Seizure outcome of the new referred cases at CCEC  
during year 2554-2557



Seizure outcome after surgery at last visit





# **Long-term courses of Juvenile myoclonic epilepsy (JME)**

# JME

- Original report on JME, published in 1957, Janz and Christian highlighted the **rarity of spontaneous remission**, as well as the **high risk of relapse after AED discontinuation**
- Further studies with follow-up periods not longer than 5 years confirmed the initial observation
- Based on 3 recent population-based studies with long-term follow up varying from 25 to 63 years after epilepsy onset
  - 24, 31, and 66 patients respectively (2009, 2012, 2013)
  - 78%, 67.7%, and 59.1% achieved seizure remission
  - **25%, 28.6%, and 28.2% were seizure-free off medication for at least the last 5 years**

*Camfield CS and Camfield PR; Neurology 2009*  
*Geithner J et.al; Epilepsia 2012*  
*Senf P et.al; Neurology 2013*

# Predictors for seizure recurrence

- **Additional absence seizure at onset of JME**
- **GTCs preceded by bilateral myoclonic seizures**
- **A long duration of epilepsy with unsuccessful treatment**
- **AED polytherapy**
- **Occurrence of photoparoxysmal responses**



**Thank you for your attention**