19th Annual Scietific Meeting of the Epilepsy Society of Thailand
July 23rd-24th, 2015, Sukosol Hotel, Bangkok, Thailand

Surgical Management for Difficult to Treat Epilepsy

Byungin Lee, M.D.

Professor of Neurology

Yonsei University College of Medicine

Seoul, KOREA

Treatment of Epilepsy

- **Primary Treatment: Pharmacotherapy(AEDs)**

- ***Alternative Treatment***
  - **Surgery**
  - Ketogenic Diet & other diet therapy
  - Behavioral therapy
    - Avoidance or stimulation alteration in Reflex epilepsy
    - Alternative sensory stimulation
    - EEG biofeedback
    - Psychological treatment
  - Traditional or Folk medicine

Surgical Procedures in Epilepsy

♣ Resective (or curative) Surgery

- Temporal lobectomy: standard or tailored ATL
- Selective amygdalohippocampectomy
- Corticectomy (or topectomy)
- Multi-lobar resection
- Hemispherectomy
- Lesionectomy

♣ *Disconnective (or palliative) Surgery*

- Corpus callosotomy
- Multiple subpial transection (MST)

♣ *Neurostimulation (or neuromodulation)*

- Vagal nerve stimulation (VNS)
- DBS, Cortical stimulation, TMS, etc
- Responsive electrical stimulation

Epilepsy Surgery (Resective)

Goal

- Seizure freedom and normalization of QOL
- In children: improve neurodevelopment

Principles

- Complete resection or disconnection of Epileptogenic zone
- No new neurological deficits (spare eloquent cortex)

Epilepsy Surgery : Indication & Timing

- SYNOPSIS -

I. Selection of Surgical Candidates

II. Presurgical Evaluation

III. Surgical Cases

IV. Timing of Patient Referral

I. Selection of Surgical candidates

- **"Selection of Surgical Candidates"** is based on the Risk-Benefit Assessment in individual patients (no absolute contra-indications)

- **"Basic Criteria of Surgical Candidates"**
  - Accurate diagnosis of Epilepsy Syndromes
    - ILAE-Classification
    - Epilepsy Syndromes related to Epilepsy Surgery
  - Medical Intractability
  - Patient's willingness to accept the process of presurgical evaluation and surgery
  - Careful evaluation of underlying illnesses and psychiatric comorbidities, QOL, etc.

I. Selection of Surgical Candidates

- Process of Patient Selection -

(1) Patient referral to the Epilepsy Center (First Step)

Primary Care Physician → **Epileptologists**

- ♣ Reason for pt. referral
  - Failure of seizure control
  - Deterioration of clinical condition
  - Presence of a mass lesion
  - Others
- ♣ Diagnostic Reevaluation
  - Dx of epilepsy syndrome
  - Etiology of treatment failure
- ♣ Medical Intractability, confirmed?
  - Yes, consider surgery
  - No, Systemic AEDs therapy
- ♣ Psychosocial evaluation

I. Selection of Surgical Candidates

- *Process of Patient Selection* -

(2) Referral for the Presurgical Evaluation (Second Step)

Epileptologists → **Presurgical Evaluation**

Selection Criteria for Surgical Candidates

♣ **Indications**

- *Medical intractability*
- Correct Dx of Epilepsy syndrome
  SRES > Non-SRES
- Stable psychosocial status
- *Patients having favorable predictive factors for surgery(?)*

♣ **Contra-indications**

- Degenerative or metabolic disorders
- Underlying serious medical illness
- Pseudo Sz or benign epilepsy syndrome
- Serious psychosocial handicaps*
  - Interictal psychosis
  - Personality disorder, depression, etc
  - Severe dysfunction of family dynamics

*only relative contraindications

Predictors of Surgical Candidacy

(Haque et al., Ped Neurol 2015:53:58-64)

- n=131 children with DREs who underwent in-patient VEEG

- 69 patients were determined surgical candidates

Variable	Surgical candidates if present	Surgical candidates if absent	P-value
One semiology at seizure onset	57/84 (68%)	2/47 (26%)	<0.001
Structural etiology	56/87 (64%)	13/44 (30%)	<0.001
Normal development (DQ>70)	37/59 (63%)	32/72 (44%)	0.04
Either single interictal focus of multiple foci but limited to one hemisphere on outpatient EEG	41/60 (68%)	28/71 (39%)	<0.001
Focal background EEG slowing on outpatient routine EEG	31/41 (76%)	38/90 (42%)	<0.001
Focal/hemispheric abnormality on MRI	49/59 (83%)	20/72 (28%)	<0.001

No. Predictors	Surgical Candidates
0	0/5 (0.0%)
1	2/16 (13%)
2	5/18 (28%)
3	8/26 (31%)
4	13/22 (59%)
5	21/23 (91%)
6	18/19 (95%)
7	2/2 (100%)

Effect	Point Estimate	95% Wald Confidence Limits
MRI abnormality	12.798	(4.712, 34.763)
Single semiology at seizure Onset	4.834	(1.836, 12.726)
Male gender	4.326	(1.624, 11.527)
Number of additional predictors	2.902	(2.040, 4.129)

❖ Only 5% (3/56) of patients with focal MRI findings had non-congruent semiology and/or interictal EEG

I. Selection of Surgical Candidates
Medical Intractability: *A Key Issue*

- **Theoretical Definition**
  - ❖ "Seizures not responding to adequate trials of all available AEDs in monotherapy and combination therapy"

- Is there any **"Unified Definition"** for practice? No!
  - ❖ **Problems**
    - Epilepsy : heterogeneous condition having different etiology, natural courses, and prognosis
    - Great individual variation among same epilepsy syndrome
    - Different definition for purpose of investigations

Medical intractability
- Pharmacological definition -

♣ ILAE Consensus Proposal *(Kwan et al., Epilepsia 2010)*

- **Failure of adequate trials of 2AEDs**
  - Well tolerated
  - Appropriately chosen and used (either monotherapy or combination therapy)

- **Failure to achieve sustained seizure freedom**
  - ≥ 3 times of the longest interseizure interval or ≥ 1year (choose the longer one)

1. Optimal AEDs Therapy

(4) AEDs Therapy after Failure to Two AEDs

♣ ***Berg et al.*** *(Ann Neurol 65:510-519)*

- ◊ n=128; f/u for 10.1yrs (med) after failure to first 2 AEDs.
- ◊ Sz remission ≥ 1yrs in 73(57%) patients

→relapse in 50 of 73 pts (68%) but often regained remission
→terminal 1yr remission in 48 (38%)
→terminal 3yr remission in 28 (22%)
→Prognostic factor : for ≥ 1yr remission : idiopathic epilepsy (RR 3.64, p<0.0001)
low Sz frequency (RR 2.57, P=0.008)
for ≥ 3yr remission : symptomatic epilepsy (RR 0.76, p=0.003)
(33% *vs.* 11% : RR=0.76, p=0.003)

♣ ***Wirrell et al.*** *(Epilepsia 2013:54:1056-1064)*

- ◊ 79 of 381 children (19.7%) : "early medical intractability" defined as
  (i) Sz freq>1/6 mo, and (ii) failure to ≥ 2 AEDs within 2 yrs of diagnosis
- ◊ Long-term outcome (median f/u = 11.7 yrs)
  34(45.3%) remained medically intractable
  34(45.3%) SF with or without AEDs
  7(9.3%) rare Szs only
- ◊ Neuroimaging abnormality: Sz free in 9%(*vs.* 60% in normal NI)
  the single important predictor of enduring medical intractability (RR:7.0, 95% CI= 2.30-21.24, p=0.0006)

Medical Intractability

- Conclusion -

- Failure to adequate trials of 2 AEDs
  - ***Recommended Criteria*** *for referral to Surgery in Lesional Epilepsy*
  - ***Minimal Criteria*** *for Refractory Epilepsy for their referral to Epilepsy Center*

- ***Conventional Criteria*** *for Refractory Epilepsy ; failure to 6-7 AEDs*

II. Presurgical Evaluation

1. Purpose

- **Localize the "Epileptogenic Zone (EZ)"**
  - brain area essential and sufficient for generation of Sz
  - hypothetical zone
    - ❖ Usually identified by convergence of independent investigating modalities or related zones
    - ❖ confirmed only after surgery
- **Determine the extent of resection**
  - the extent of EZ and its relation to the eloquent cortex

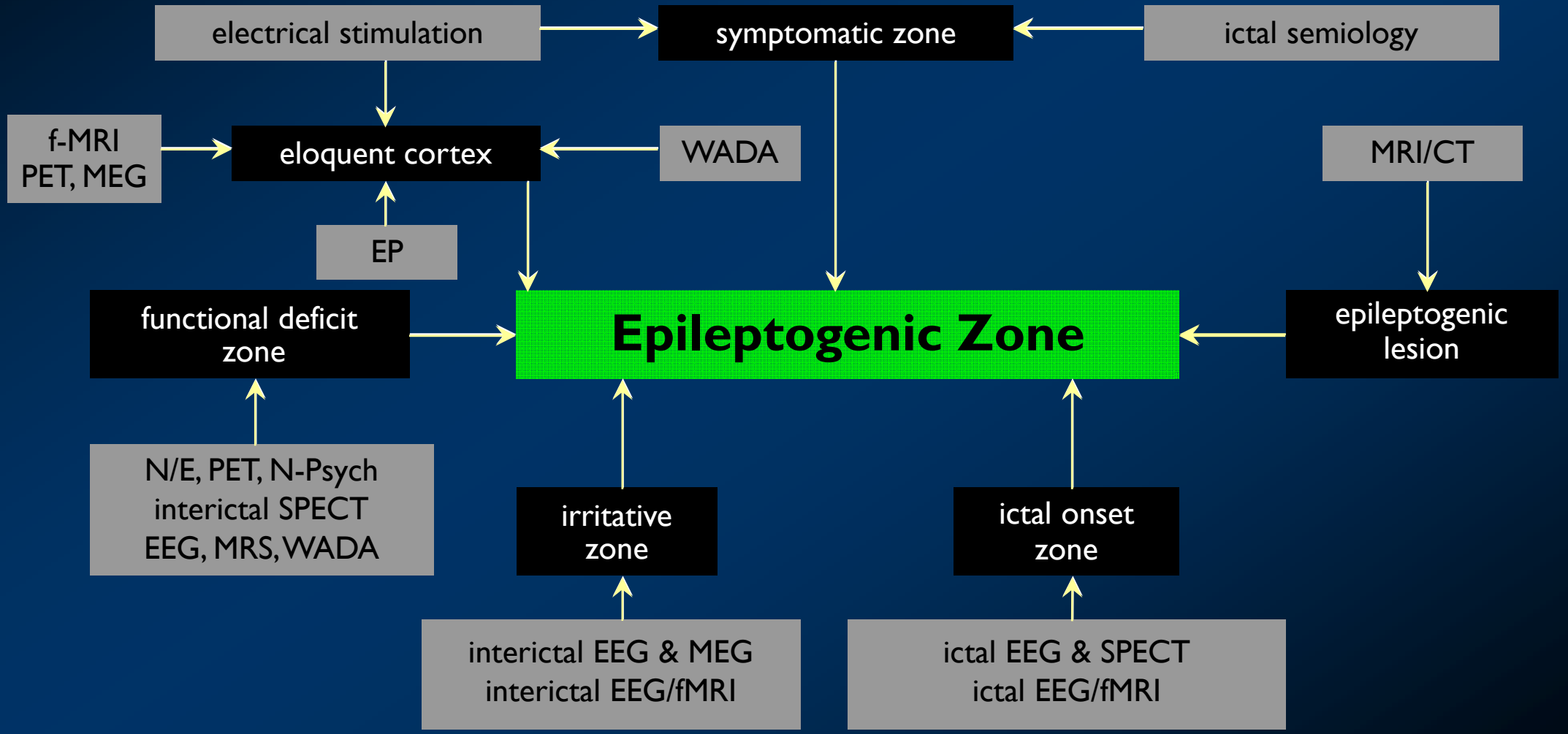
How to Localize "Epileptogenic Zone" ?

- Related Zones -

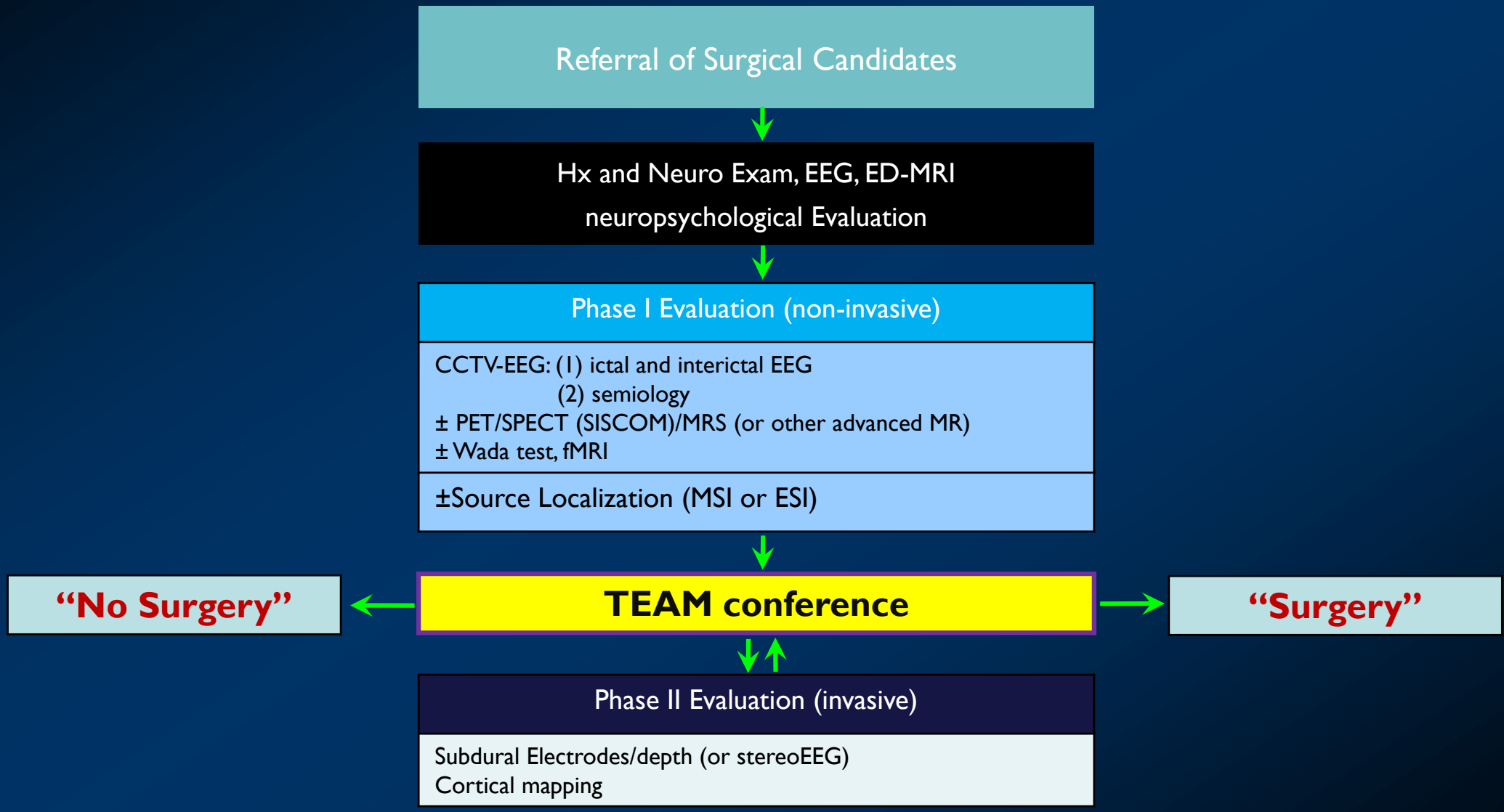
Descriptions of Zones and lesions of the cortex (Lüders and Awad, 1992)	
Epileptogenic zone	Region of cortex that can generate epileptic seizures Total removal or disconnection of the EZ is necessary and sufficient for Sz-freedom
Irritative zone	Region of cortex that generate IEDs
Seizure onset zone	Region where the clinical seizures originate
Epileptogenic lesion	Structural lesion that is causally related to the epilepsy
Ictal symptomatic zone	Region of cortex that generate the initial Sz symptoms
Functional deficit zone	Region of cortex that is functionally abnormal during interictal period
Eloquent cortex	Region of cortex that is indispensable for defined cortical functions

II. Presurgical Evaluation

2. General Concepts



Pathway of Epilepsy Surgery

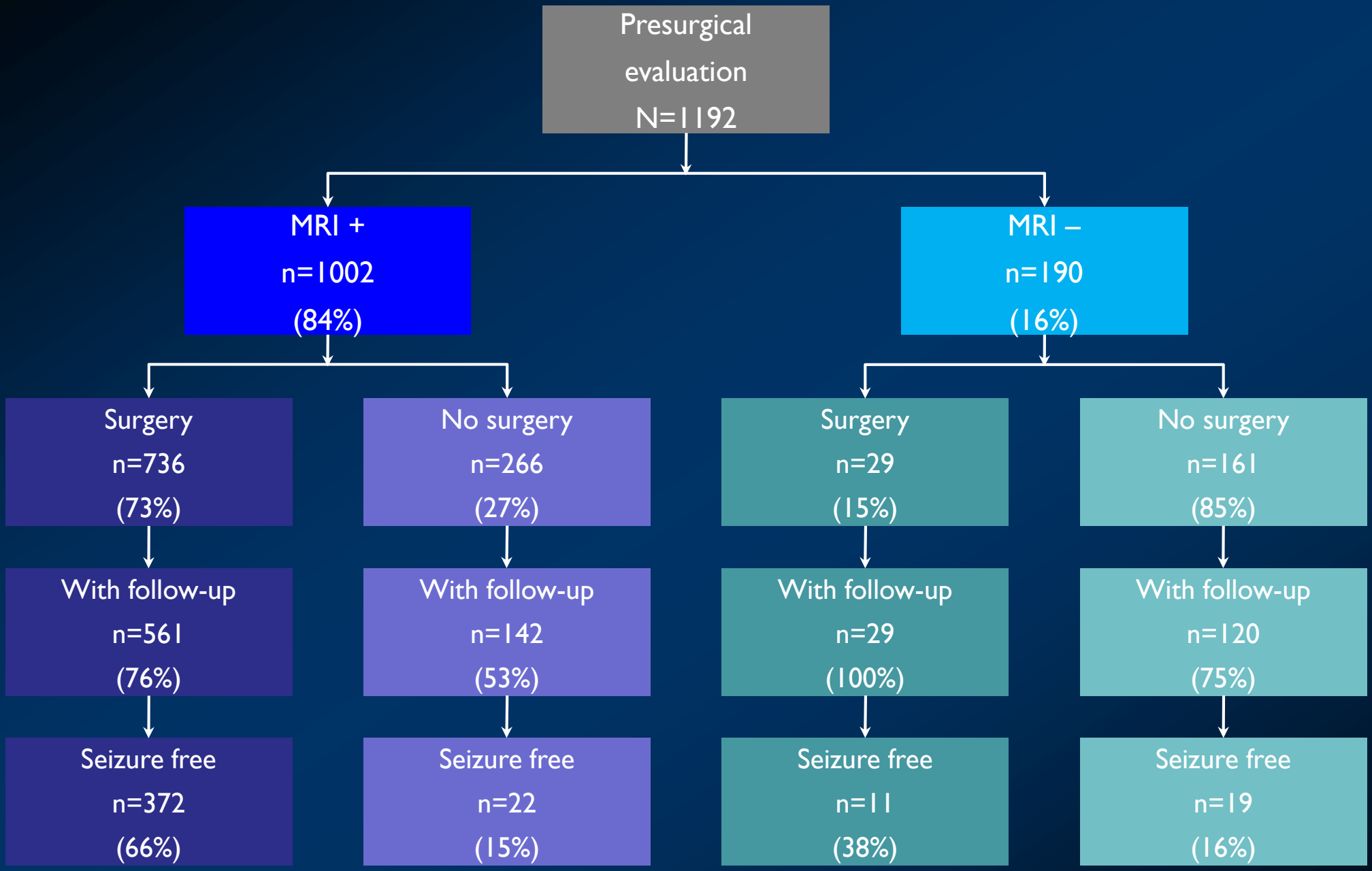


Surgical Outcomes

- **Literature Review Published since 1995**
  - **Tellez-Zentano et al. (Epilepsy Res. 2010:89;310-318)**
    - 40 articles, Non-lesional (n=697) vs Lesional (n=2860) cases
    - SFR based on presurgical MRI

Categories	Non-lesional			Lesional		
	N	SF(%)	95% CI	N	SF(%)	95% CI
Temporal lobe	226	51	45-57	514	75	71-89
Ext-TLE	124	35	27-42	225	60	54-66
TLE+Ex TLE	398	46	41-51	965	70	68-73

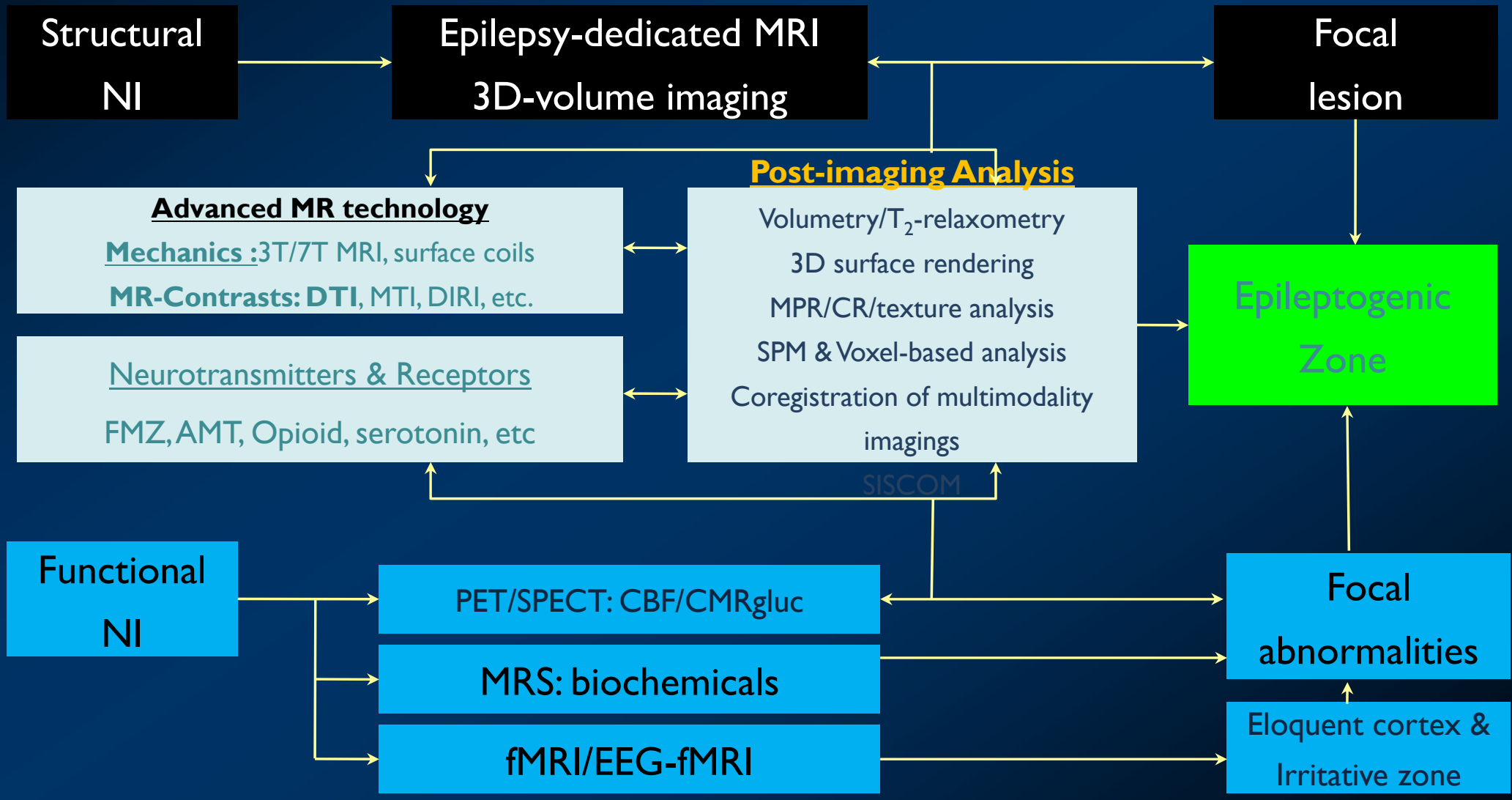
    - the odds of being Sz free after surgery was 2.5 times higher in patients with LE.

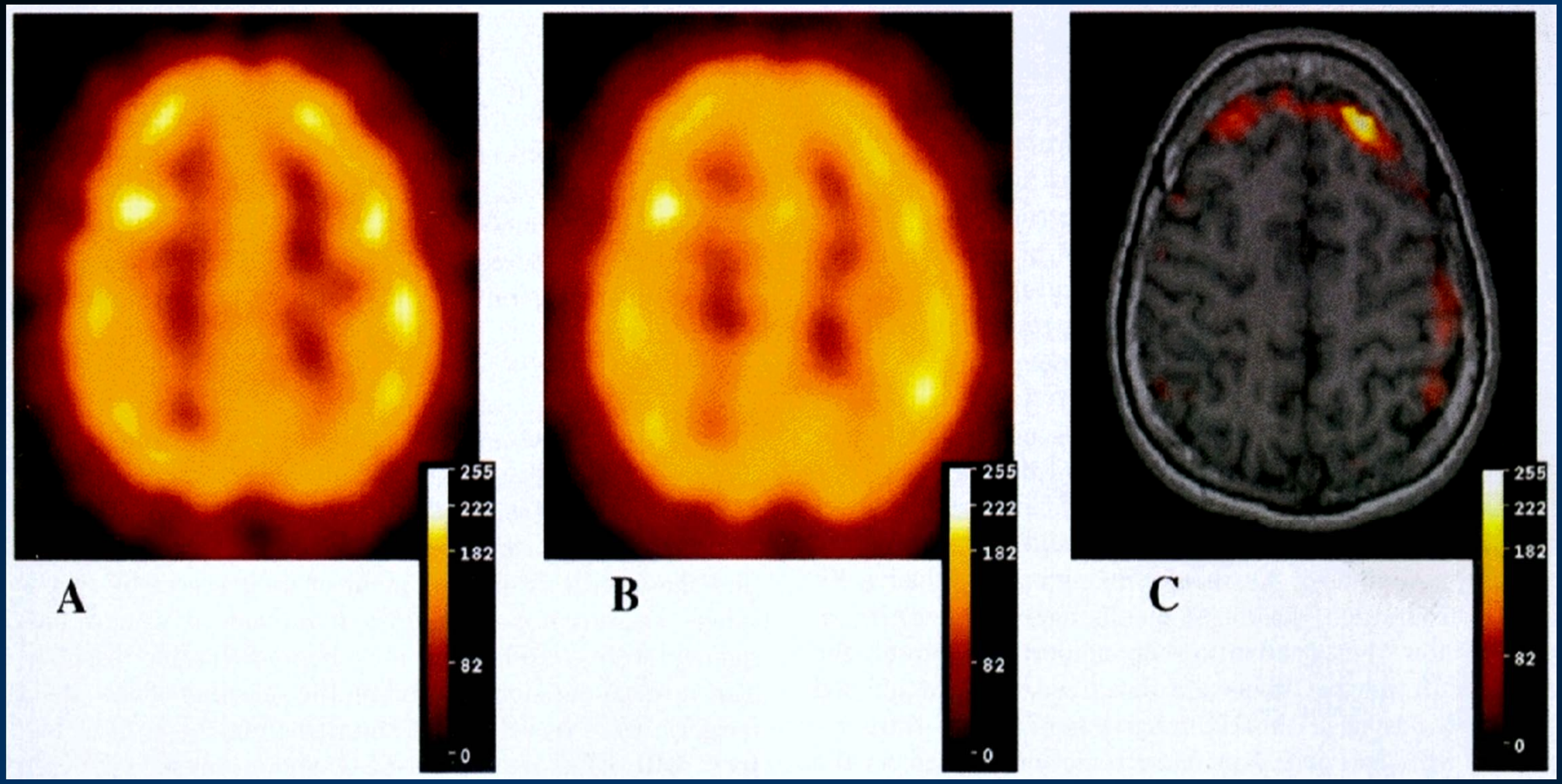


Overview of all presurgically evaluated patients and their outcomes

Bien et al., Arch Neurol 2009;66:1491-1499

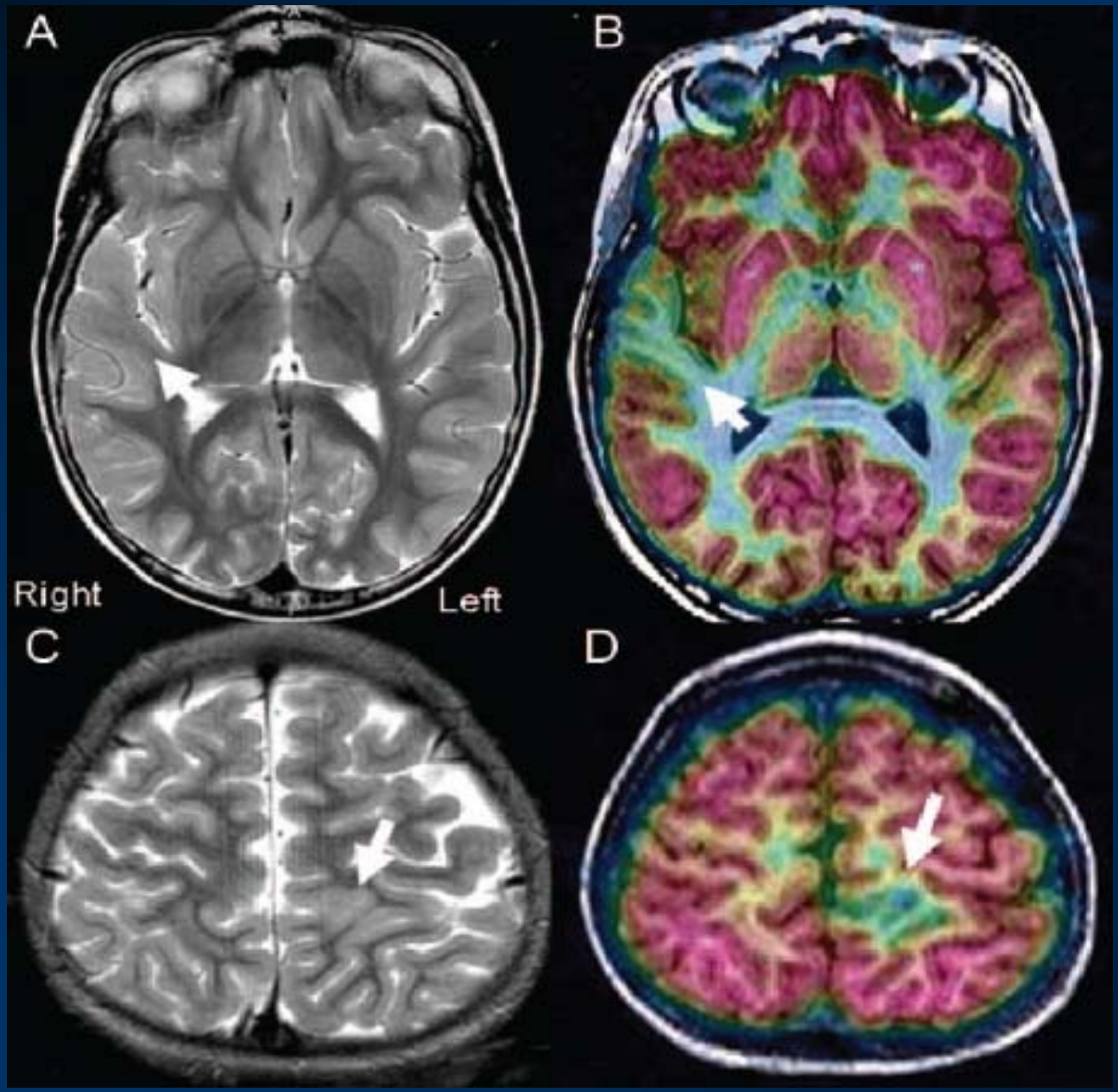
Neuroimaging Modalities for Epilepsy Surgery





Ictal (A) and interictal (B) SPECT and SISCOM (C) images from a patient with intractable seizures with a normal seizure-protocol MRI. Ictal SPECT showed a number of high-intensity areas, including those in the left frontal, right frontal, and left parietal regions. Using the traditional visual method of reviewing SPECT images, blinded reviewers determined the scans to be nonlocalizing. However, using SISCOM images, the reviewers localized the focus of hyperfusion to the left frontal area. Left frontal lobectomy was performed after confirmation of the site of seizure onset with intracranial EEG. The patient was seizure free at 22 months after surgery.

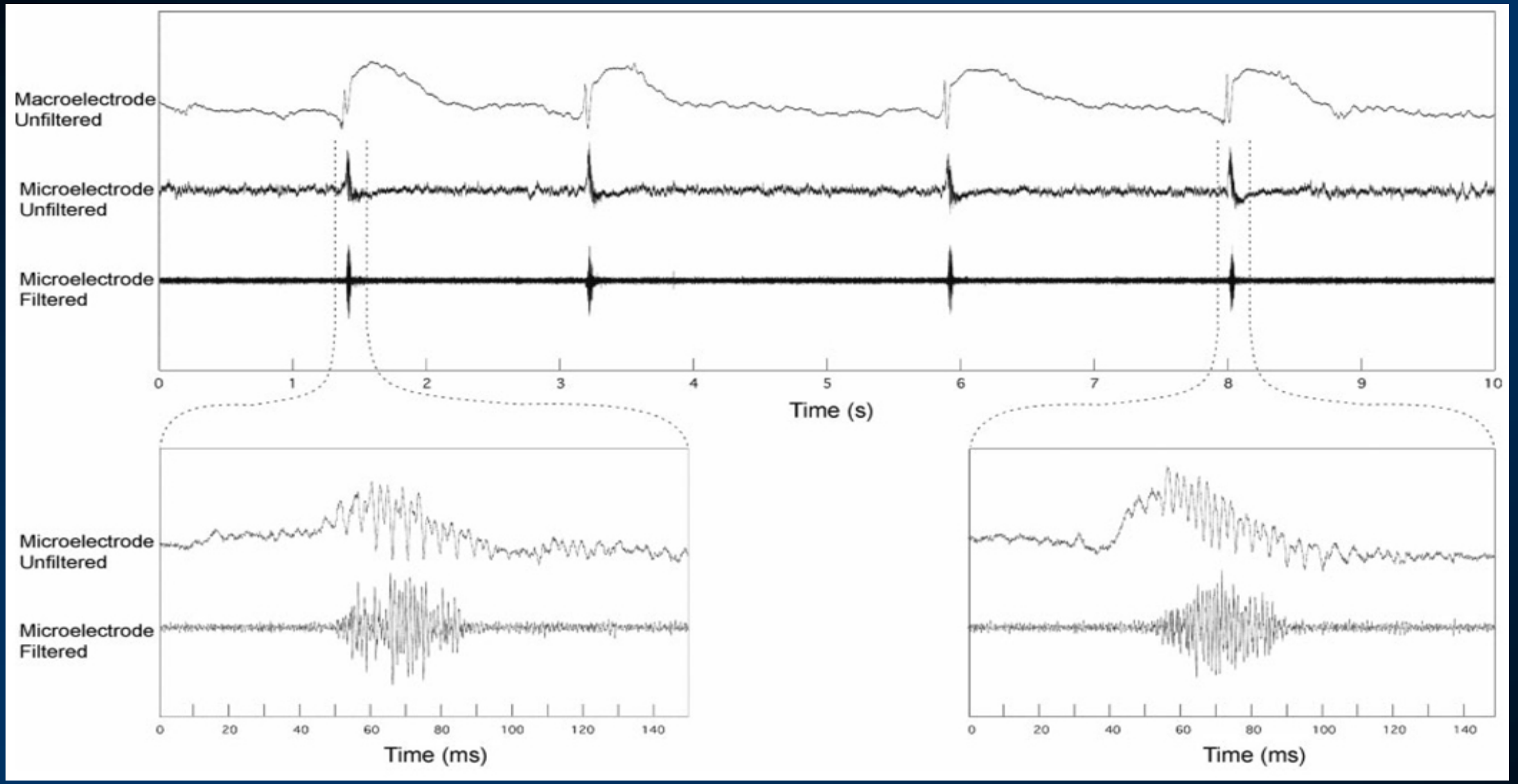
(O'Brien et al., Neurology 1998 ; 50 : 445-454)



Examples of difficult-to-identify type I cortical dysplasia from two patients with epilepsy

(Salamon et al. Neurology 2008;71:1594-1601)

High-frequency oscillations in human



Worrell et al., (Brain 2008;131:928-937)

High-frequency Oscillation (HFO)

- **Fast Ripples --- A biomarker of epileptogenic zone?**
  - Found only in Rats exhibiting spontaneous seizures after epileptogenic insult (SE models)
  - Associated with sites of Sz onset
  - A greater number of FR-generating sites correlates with a higher rate of Sz.

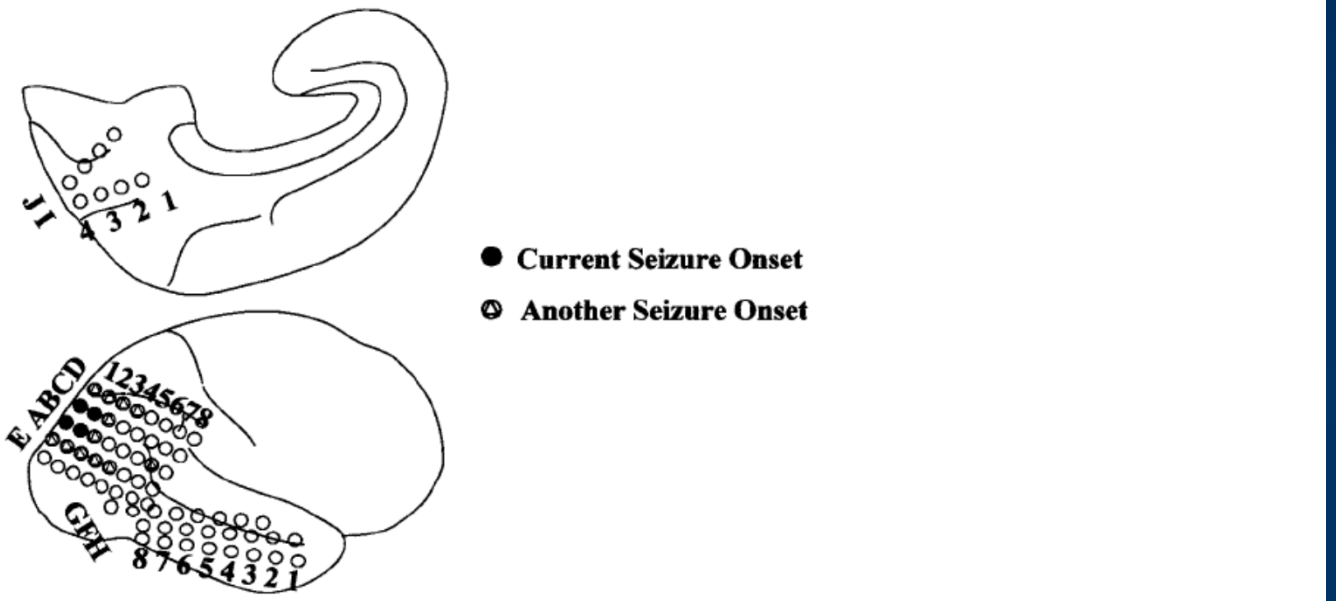
(Bragin et al., current opinion in Neurology 2010; 23: 151-156)

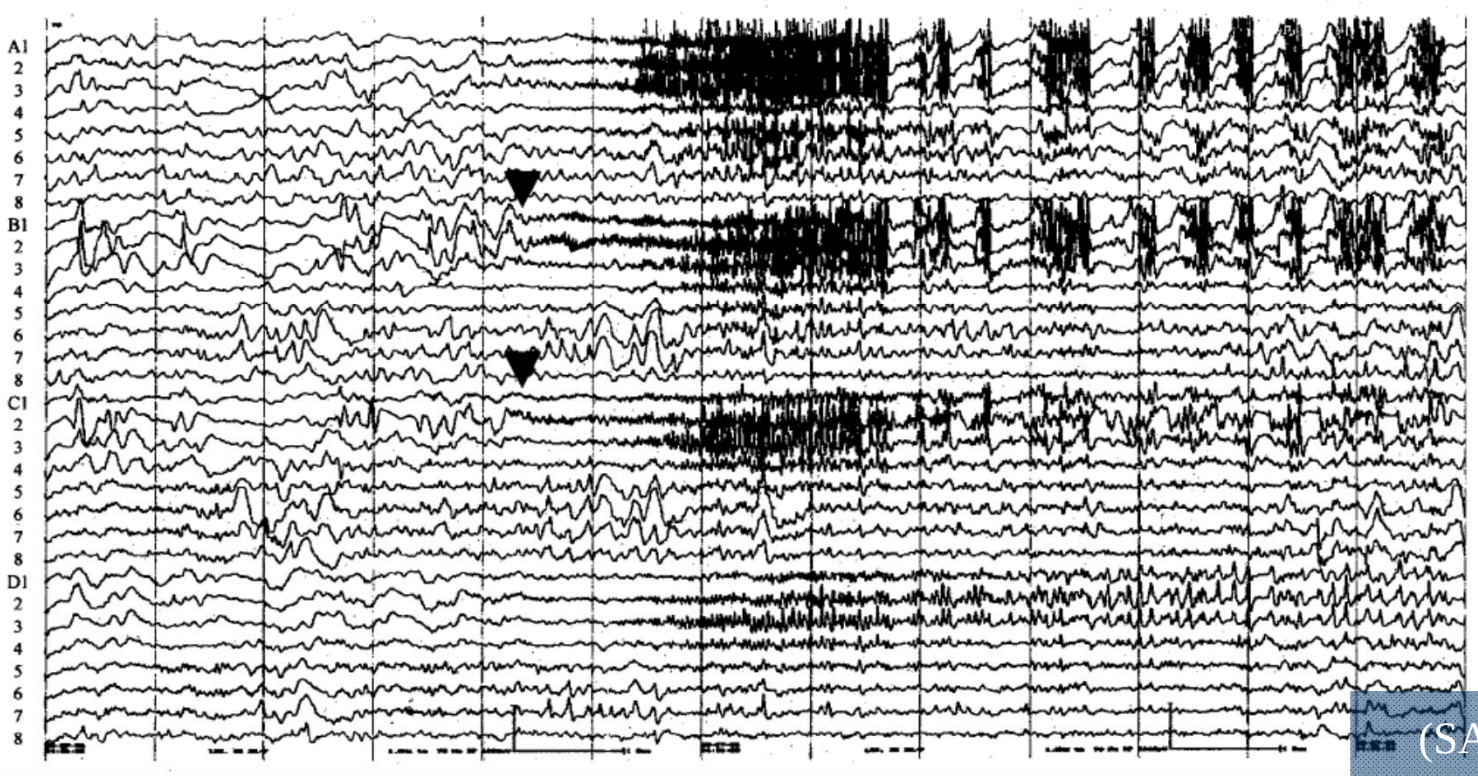
- **Fast Ripples and Epilepsy Surgery**
  - Removal of brain tissue exhibiting preoperatively recorded HFOs was associated with better surgical outcomes *(Jacobs et al., Ann Neurol 2010;51:573-582)*
  - Residual FRs in post-resection ECoG were associated with higher seizure recurrence rate after surgery, but not with ripples, interictal spikes, and ictiform spikes

(von't Klooster et al., Neurology 2015; 85: 120-128)

- **Is it time to replace epileptic spikes with fast ripples?**

(Jobst and Engel, Neurology 2015;85:114-115)





(SA Park et al. Epilepsy Res 2002:48)

- Team Conference -

♣ *An integral part of pre-surgical evaluation*

- Each patients present unique management situations
- Multi-disciplinary team approach to synthesize complex objective and subjective data
- Concordance of independent data(semiology, imaging, EEG) – Key for determination of Epileptogenic Zone

♣ *Basic Issues*

- Is the EZ well localized?
  - If yes (i) can the EZ be resected safely?
    (ii) any risks for its complete resection?
  - If not, what is the next step? Synthesis of hypothesis
    (i) can phase II investigation reliably localize the EZ?
    (ii) what is the hypothesis for the choice and placement of intracranial electrodes?

Surgery of Non-lesional Partial Epilepsies

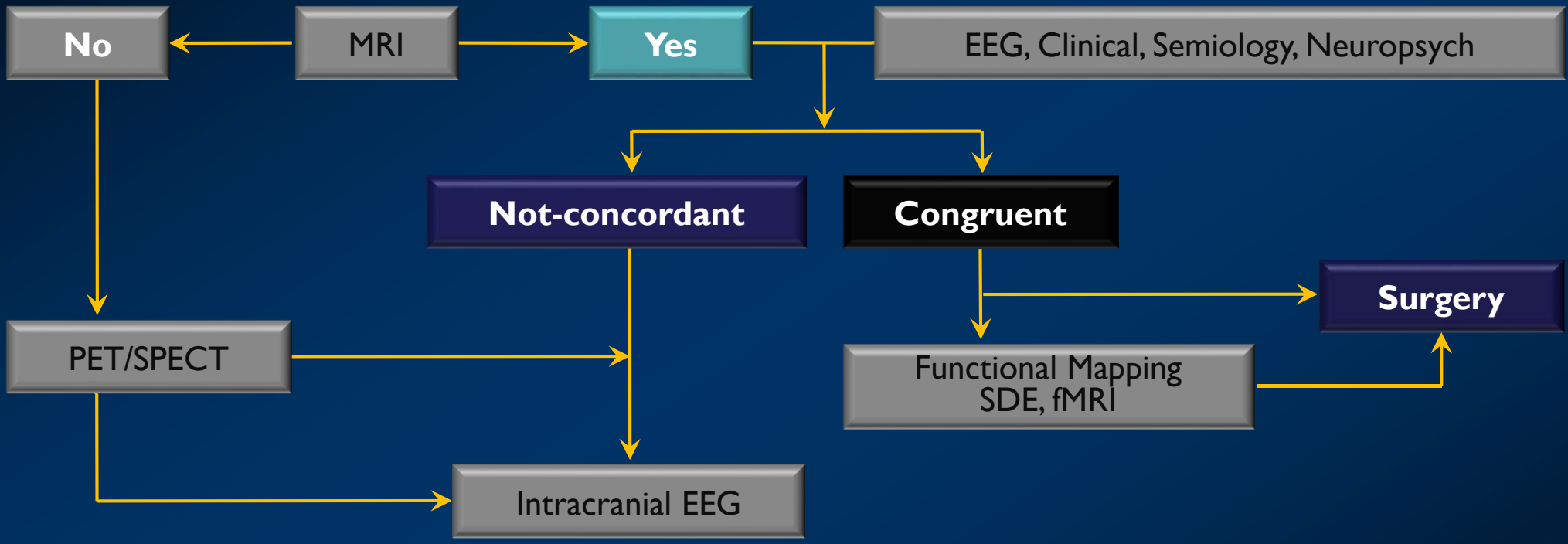
♣ SK Lee et al. (Ann Neurol, 2005)

n=89, Sz free rate : 47% at f/u ≥ 2yrs

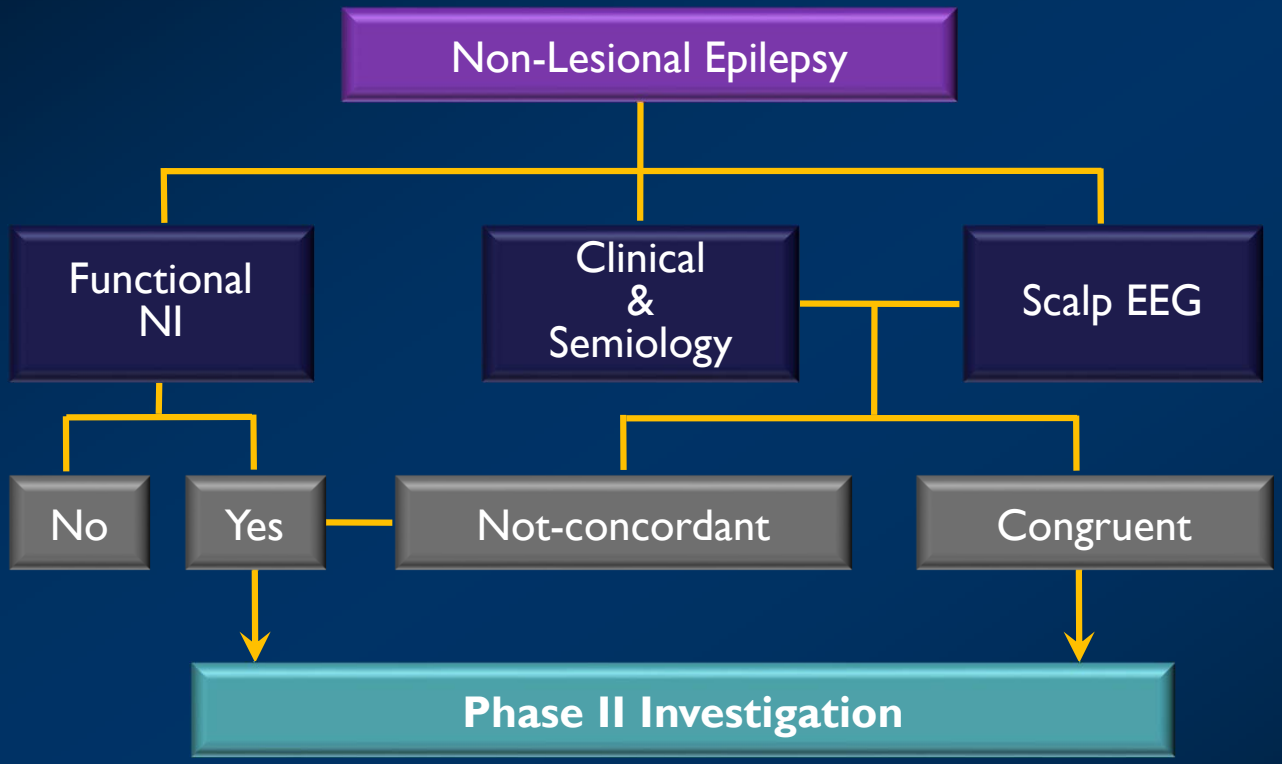
Comparison of concordance rates of individual tests

concordance (number of patients)	Sz-free (42)	not Sz-free (47)
four modalities (5)	4(80%)	1
three modalities (18)	10(56%)	8
two modalities (25)	15(60%)	10
one modality (28)	9(32%)	19
all non-localizing (13)	4(31%)	9

MRI-based Algorithm of Epilepsy Surgery



Presurgical Evaluation in Non-lesional Epilepsy



CASES(1-3)

IV. Time to Epilepsy Surgery

- **No specific Guidelines** for optimal timing for surgery
- **Expert's opinions** are centered at **avoidance of unnecessary time delay** in patient's referral to surgery
- **Early surgery of MTLE** (≤ 2 yrs after failure of 2 AEDs) were found to be effective

IV. Time to Epilepsy Surgery

1. Current status

Duration between Age at onset and Presurgical evaluation

Authors	Sites	n	Age at surgery	Epilepsy duration (years)
Spencer et al. (2005)	(Multicenter)	396	37	22
Gilliam et al. (1999)	University of Alabama, Brimingham	196	32	19
Wiebe et al. (2001)	Ontario	80	35	22
Choi et al. (2009)	New York	213	35	22

Gilliam & Albertson, Epilepsy Behav 2011;20:156-159

IV. Time to Epilepsy Surgery

1. Current status

♣ Any changes in referral patterns since the publication of AAN practice Parameter (2003)?

Haneef et al. (Neurology 2010;75:699-704)

- Analysis of patients with TLE referred for 1995 to 1998 (group 1, n=83) and 2005 to 2008 (group 2, n=102)
- No difference between Group1 vs Group 2
  - Duration of illness 17.1±10.0 18.6±12.6 yrs (p=0.39)
  - Age of evaluation 34.1±10.3 37.0±11.8 yrs (p=0.08)

- Conclusion : (i) No impact of AAN practice parameter on the practice of patients referral for surgery
  (ii) Need more efforts for communications with primary physicians about epilepsy surgery

IV. Time to Epilepsy Surgery

2. Barriers to Earlier Patient's Referral

- Shortages of Evidence for the advantage of Early Surgery
- Time delay until confirm the **"Medical Intractability"**
- Attitude of Stakeholders
  - Referring physicians
  - Epilepsy Experts
  - Patients and family
- Others

2. Barriers to Earlier Patient's Referral

(1) Early Surgery in MTLE

Engel et al., JAMA 2012;307:422-430

- n=38 (23 pts: med Rx, 15 pts: ATL)
  - MTLE within 2 yrs after the failure of adequate trials of 2 AEDs
  - In all, both MRI and PET were diagnostic of MTLE
  - Mean duration of epilepsy : 5.2 yrs(3.2 – 15.8 yrs)

- Results
  - None in medical group and 11 of 15 pts in surgical group were SF during 2 yrs of f/u ($p < 0.001$)
  - Memory decline in 4 pts (36%) after surgery
  - Transient deficit in 1 pts after surgery (MRI-identified stroke) and SE in 3 pts in medical group
  - QOL: higher in the surgical group but NS (p=0.08)

- Conclusion
  - Surgery soon after failure of 2 AEDs offers better chance of preventing a lifetime disability
  - No evidence for long-term outcomes of QOL, cognition, and psycho-social function, etc.

2. Barriers to Earlier Patient's Referral

(2) Time Delay until Confirm of Medical Intractability

- Natural courses of epilepsy are often variable and repeat remissions and relapses
  - ✓ *Sillanpaa and Schmidt (Brain, 2006)*: n =144 (children)
    - ❖ late remission (mean 9 years) in 50%
    - ❖ remission and relapses in 33%

- *Borodie et al. (Neurology, 2012)*: n =1098 (mixed)
  - ❖ delayed remission in 22%
  - ❖ remissions and relapses in 16%

2. Barriers to Earlier Patient's Referral

♣ *Berg et al., Neurology 2003;60:186-190*

- n= 333: A Multicenter Study of Surgical outcomes
- Criteria of Intractability
  - ≥ 20 CPS during the 24 mo prior to presurgical evaluation
  - Failure of ≥ 2 first-line AEDs
- Result :
  - Latency time from Sz onset to the Dx of RE: 9.1 years (0 to 48 yrs)
  - 26% reported a prior remission (≥ 1yr) before the Dx of RE with Remission ≥ 5yrs in 85%
  - Young age of onset has associated with longer latency time ($p<0.0001$) and higher probability of past remission ($p<0.001$)

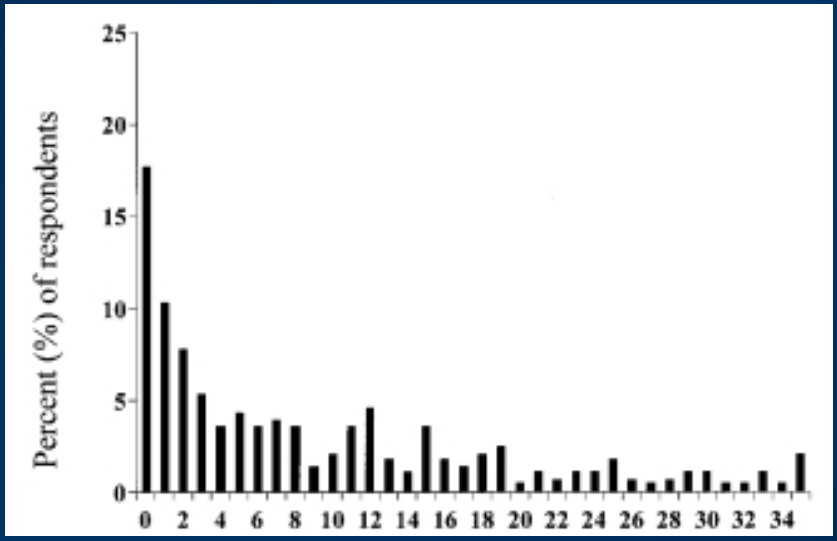


Fig. Distribution of time from second unprovoked seizure to failure of second medication (intractability) in 333 surgical patients

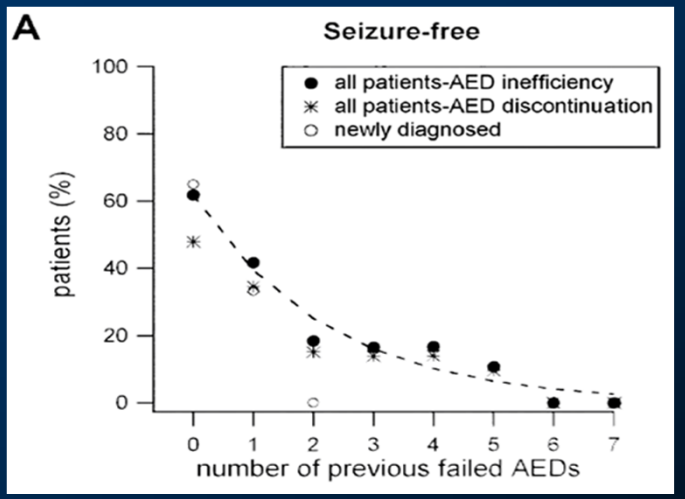
Pharmacotherapy in Drug Resistant Epilepsy

Luciano and Shorvon (Ann Neurol. 2007)

- N=155; ≥ 1 Sz/mo; Sz duration ≥ 5yrs
- 265 trials of drug addition (new AEDs)
  - SFR in 28% of all patients
  - SFR of 16% of all drug introduction
- Predictors of SF: number of failed drug (<5 drugs), IGE, duration of epilepsy (<10yrs)

Schiller and Najjar (Neurology 2008;70:54-65)

- N=478; newly treated; f/u: 1.5 to 7.5 yrs
- SFR: 61.8% for the first drug
  41.7% for the 2nd drug
  16.6% for 3rd-6th drug
  0 % for 7th drug or more
- Predictors of SF: number of failed drug, IGE
  duration of epilepsy, No of Sz prior to AED therapy



IV. Time to Epilepsy Surgery
2. Barriers to Earlier Patient's Referral
(3) Attitudes of Stakeholders

- Survey of Neurologists *(Hakimi et al., Epilepsy & Behav 2008;13:96-101)*
  - N=84 (Michigan, USA)
  - Results : 3 major factors for delay in patients referral

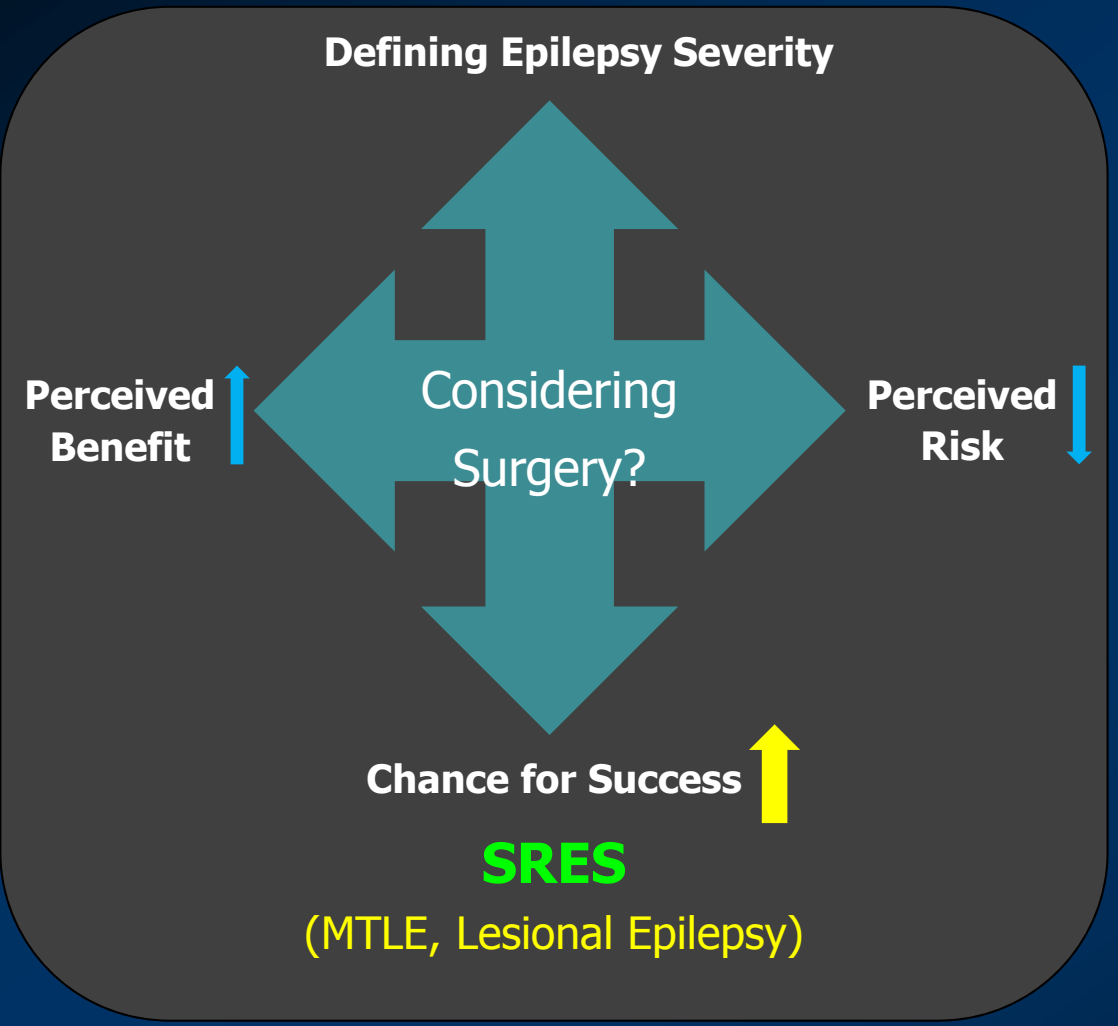
(i) more conservative definition of medical intractability
- Failure of ≥ 3 drugs for monotherapy and combination therapy

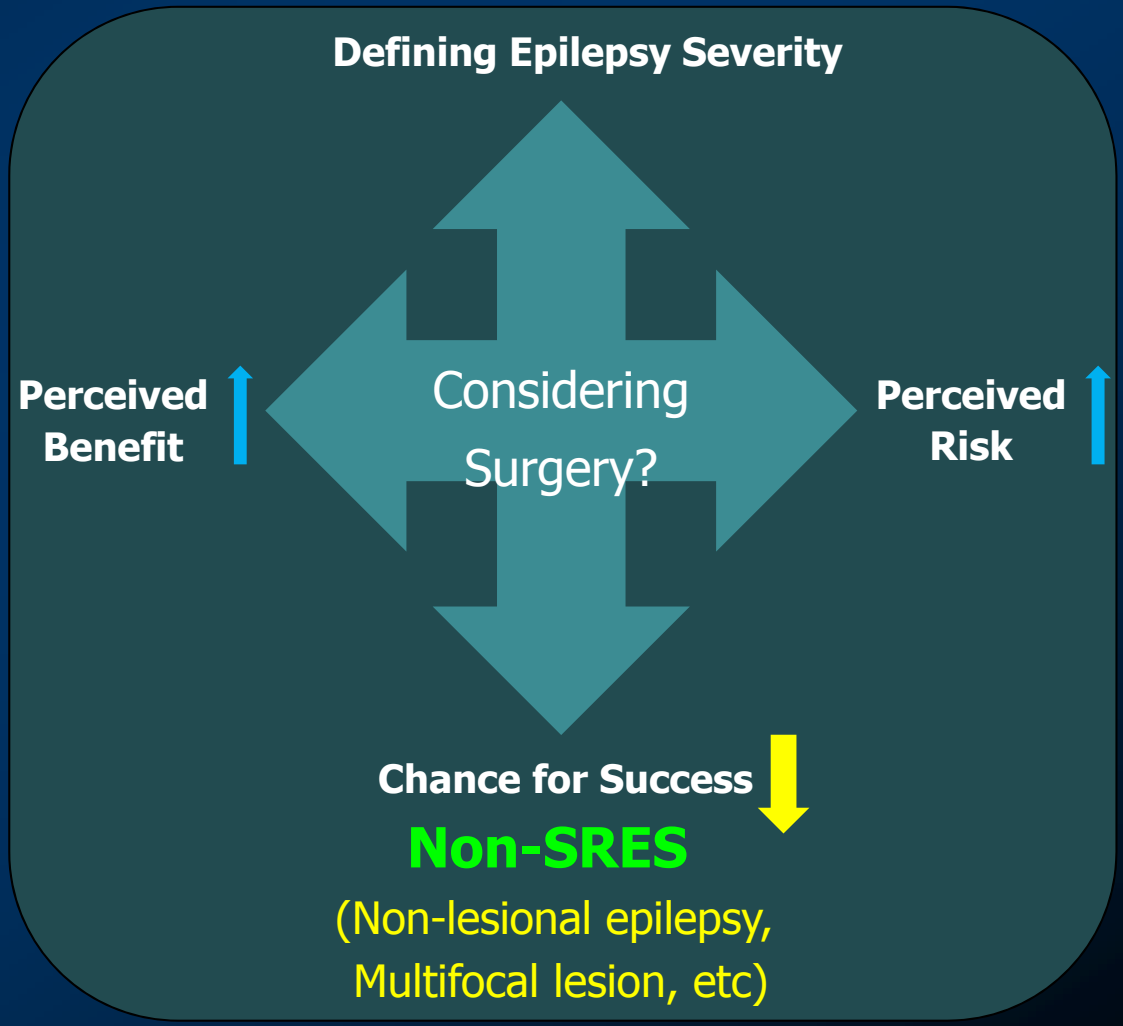
(ii) Knowledge on Surgical outcomes
- Only 27% reported Sz. Free rate > 70%, while 60% reported the complication rate is > 5%
- 31% reported that patients experienced serious post-op complications

(iii) Lack of Communications from the Epilepsy Centers
- 47% reported no appropriate feedback from the epilepsy center about their patients
- 38% reported no return of their patients in a timely manner

IV. Time to Epilepsy Surgery

3. Competing Factors for the "Decision of Epilepsy Surgery"





Modified from Gilliam & Albertson, Epilepsy Behav 2011;20:156-159

IV. Time to Epilepsy Surgery
4. Experts Opinion

- In situations where surgery can produce a high remission rate,
  - It is advisable to recommend a surgical procedure
  - ATL or lesionectomy

- In situations of normal MRI and a probable extrahippocampal origin
  - Not best served by immediate surgery after failure of only two medications
  - It is advisable to recommend further trials of AED therapy
  - Higher surgical risk
  - Low chance (25%) of inducing long-lasting seizure remission

Kwan & Sperling, Epilepsia 2009;50:57-62

Thanks for your attention