

**SREE CHITRA TIRUNAL INSTITUTE FOR
MEDICAL SCIENCES AND TECHNOLOGY**
THIRUVANANTHAPURAM, KERALA



**LONG TERM SURGICAL OUTCOME AND
PREDICTORS IN POSTERIOR CORTEX EPILEPSY**

Dissertation submitted in partial fulfilment of the rules and regulations for
awarding the degree of

Post-Doctoral Fellowship in Epilepsy

Sree Chitra Tirunal Institute for Medical Sciences and Technology

By

Dr Harini Pavuluri

Postdoctoral fellow, Epilepsy

Month and Year of Submission: December 2022

R Madhavan Nayar Centre for Comprehensive Epilepsy Care

Department of Neurology

Sree Chitra Tirunal Institute for Medical Sciences and Technology

Thiruvananthapuram

01/01/2022 to 31/12/2022

DECLARATION

I, Dr. Harini Pavuluri, hereby declare that this project was undertaken by me under the supervision of the faculty, RMadhavan Nayar Centre for comprehensive Epilepsy Care, Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology.

Harini P

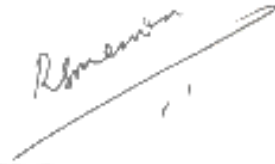
Thiruvananthapuram,

Dr. Harini Pavuluri

Date: 25-12-2022

Forwarded:

The candidate Dr Harini Pavuluri has completed the project under my guidance



Thiruvananthapuram

25/12/2022

Dr Ramshekhar N Menon

Professor and In-charge

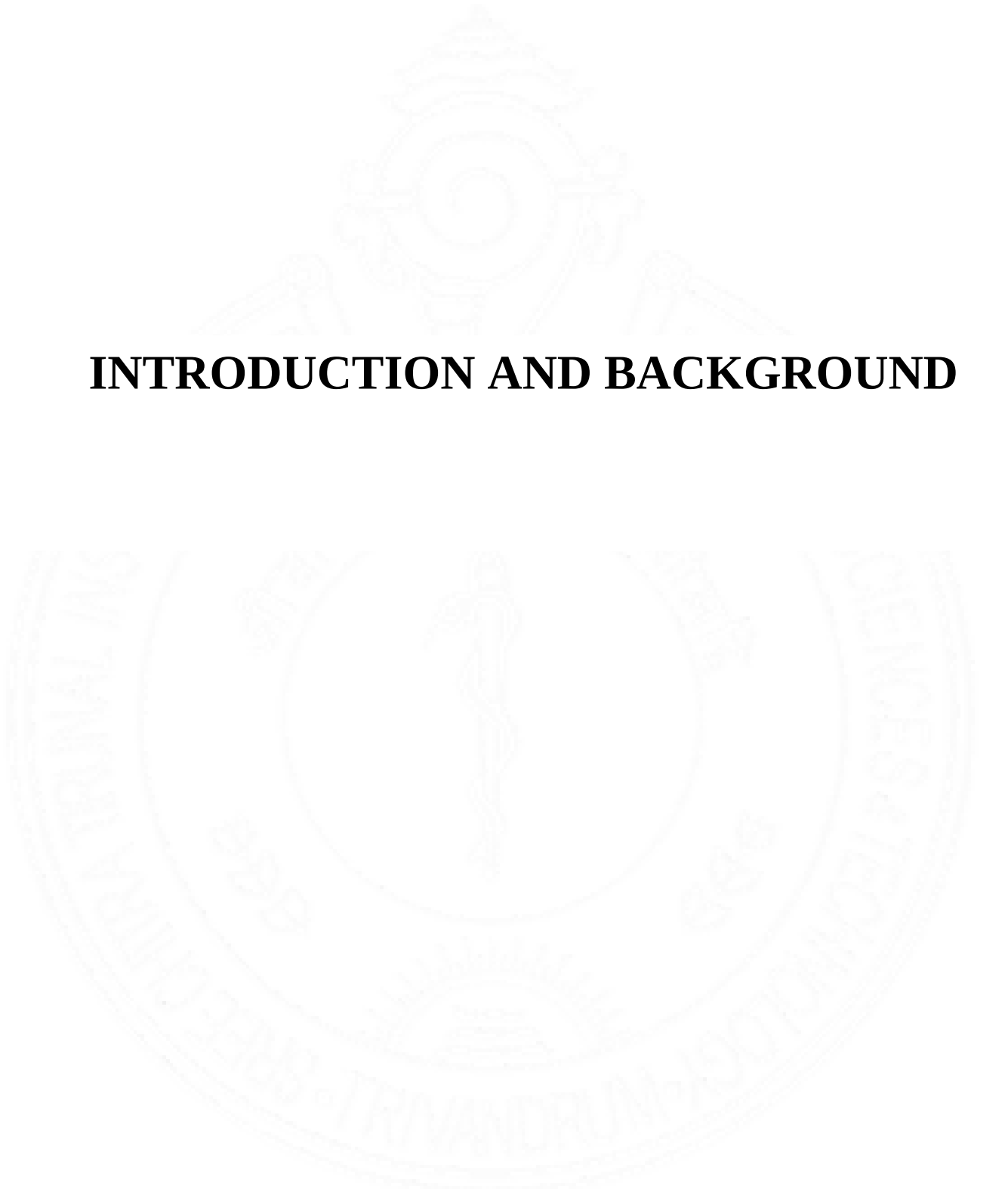
R Madhavan Nayar Centre for
Comprehensive Epilepsy Care

Department of Neurology

SCTIMST

INDEX

i.	Background and Introduction	5-7
ii.	Review of Literature	8-15
iii.	Aims and objectives of the study	16
iv.	Methods	17-23
v.	Results	24-40
vi.	Discussion	41-48
vii.	Conclusions	49-50
viii.	References	51-53
ix.	Annexures	54
	a. Abbreviations	54
	b. Proforma	55-58
	c. Institutional Ethics Committee approval	59-60
	d. Plagiarism check	61



INTRODUCTION AND BACKGROUND

Posterior cortex epilepsy is a multi-lobar epilepsy syndrome involving seizures arising from either the temporal, parietal, or occipital lobes, individually or in combination. It is less common compared to temporal and frontal lobe epilepsies but is often very debilitating with high rates of drug resistance, causing significant morbidity and poor quality of life. The etiological spectrum includes metabolic, structural, neoplastic, traumatic, infective, and idiopathic causes(1). Neuroanatomic and physiological distinctions between these areas is usually less marked and accurate source localisation of the epileptogenic region is often difficult in these regions. In addition, the proximity to the visual cortex carries an inherent risk of visual loss following surgery(2–4). For the above reasons, surgical management of the posterior cortex epilepsy surgeries is less frequent constituting <10% of all the epilepsy surgeries with relatively poorer outcomes compared to temporal lobe epilepsy. Seizure freedom rates varied between 25-90% across various studies with no clear agreement among each of them(1–5). The various predictors for poor outcome identified in earlier studies include partial resections, parietal lobe resections, ipsilateral temporal spikes on EEG, postoperative spikes on EEG, baseline seizure frequency (2,3)while shorter duration of epilepsy and normal neurological examination (1), age of onset < 18 years, abnormal pre op MRI and focal lesion on pathology (4) predicted favourable outcomes.

Relevance: There have been no studies from India which looked at the surgical outcomes in posterior cortex epilepsy surgeries. While most the studies done from various centres across the world mostly looked at parietal and occipital lobe surgeries individually, there are very few studies which looked at posterior cortex epilepsy surgery series as a whole. These limited number of studies often had limited sample sizes (<100) and with no clear consensus reached upon key outcome measures like seizure outcomes and predictors . Our study would provide a comprehensive representation of posterior cortex epilepsy surgery as a whole, its outcome and predictors, from a considerably larger sample size especially pertaining to Indian subcontinent.

LITERATURE REVIEW

The earliest data on the surgical management and outcomes of refractory posterior cortex epilepsy comes from the Montreal Neurological Institute which published their series of patients (Salanova et al (6)) with refractory occipital and parietal lobe epilepsy.(6) The earliest study was published in Brain , 1992 where they elucidated the outcomes in 42 patients with refractory occipital lobe epilepsy, studied over 6 decades between 1930 and 1991. Seizure freedom i.e Class I Engel outcome was obtained in 46% while 21% had significant reduction in seizure frequency after a mean follow up duration of 17 years(6). Absence of epileptiform discharges on post resection Electrocorticography and presence of a lesion on imaging were associated with favourable outcomes. (6)

The same group subsequently published another large series of 82 patients with refractory parietal lobe epilepsy who underwent resective surgery between 1929 and 1988, spanning over 7 decades. 65% of them had a favourable outcome with complete seizure freedom or significant reduction in seizure frequency(7). Post resection spikes on Electrocorticography was an important predictor of seizure freedom in this group as well(7).

A recent meta-analysis was published by the Serbian group on the clinical features and surgical outcomes in refractory Parietal lobe epilepsy(8). This meta-analysis had included around 7 major retrospective series (9–11)(7,8,12–14)

published till date with a total sample size of around 250 patients (8). Class I Engel outcome rate was observed in 62% of the patients following a mean follow up of nearly 9 years. Interictal EEG localised to the lesion and presence of tumour as a substrate were two important predictors of seizure freedom.(8)

Another meta-analysis published recently looked at outcomes in occipital lobe epilepsy and posterior cortex including, nearly 600 patients from 27 different case series comprehensively analysed the surgical outcome and predictors involving the entire spectrum (4). A class I Engel outcome was observed in 65% of the patients. Factors predicting the seizure freedom included age less than 18 years, presence of a pathological lesion on histopathological analysis and abnormal preoperative MRI. Around 57% reported varying degrees of visual impairment.(4). Neither the type of seizure, duration of epilepsy, demographic variables, type of surgery or degree of resection predicted the outcomes.

However, these factors were of variable significance across the various studies.

Dalmagaro et al was the one of the first to study posterior cortex surgical outcomes in 81 patients and tried to assess the predictors. 65.1% had Engel class I outcome with shorter duration of epilepsy and normal neurological examination predicting a favourable outcome.(1)

One of the earliest studies published by Lara Jehi et al (15) from the Cleveland group looked at the longitudinal outcome in patients who underwent posterior

cortex epilepsy surgery with a sample size of 57 patients. Mean follow up duration was however only 3.3 years and nearly 2/3rd of them had Engel class I outcome. The important predictors identified in this study were degree of resection, site (parietal with poor outcome) and pathological substrate (tumours and dysplasia had relatively better prognosis compared to other aetiologies).

Another study by Elsharkawy et al(16) including a large sample size of around 200 patients, which looked at the long term outcome of lesional posterior cortex epilepsy surgery, identified a wide variety of clinical and electrophysiological factors that are likely to be associated with an unfavourable outcome which includes presence of a somatosensory aura, GTCS semiology, extra regional spikes, incomplete resection and spikes on post operative EEG especially at 6 months and 2 years and dysplasia as substrate in the resected specimens.(16)

The various studies looking at the outcomes in posterior cortex epilepsy surgery available till date and the key findings from the studies are summarised in the table below.

Only one study published in India was from CMC Vellore , in collaboration with multiple centres across the world in 2007 which described the variant in the surgery and outcomes. A total of 17 patients were studied with favourable outcomes in about 90%.(17)

Table 1: Summary of available literature on outcomes in posterior cortex epilepsy surgery

Study	Sample size	Mean follow up duration	Key results
Ramantani G, Stathi A, Brandt A, et al Posterior cortex epilepsy surgery in childhood and adolescence: Predictors of long-term seizure outcome. <i>Epilepsia</i> . 2017 (18)	50	2 years	60% Engel class I outcome. Left-sided and parietal epileptogenic zones and resections, longer epilepsy duration to surgery predicted recurrence
Liava A, Mai R, Cardinale F, Tassi L, et al; Epilepsy surgery in the posterior part of the brain. <i>Epilepsy Behav</i> . 2016 Nov (19)	208	9.6 years	70% Engel class I outcome; early surgery associated with higher chances of success
Liava A, Mai R, Tassi L, et al Paediatric epilepsy surgery in	62	6.94 years	85.5% Engel class I outcome; elderly age at onset, restrictive

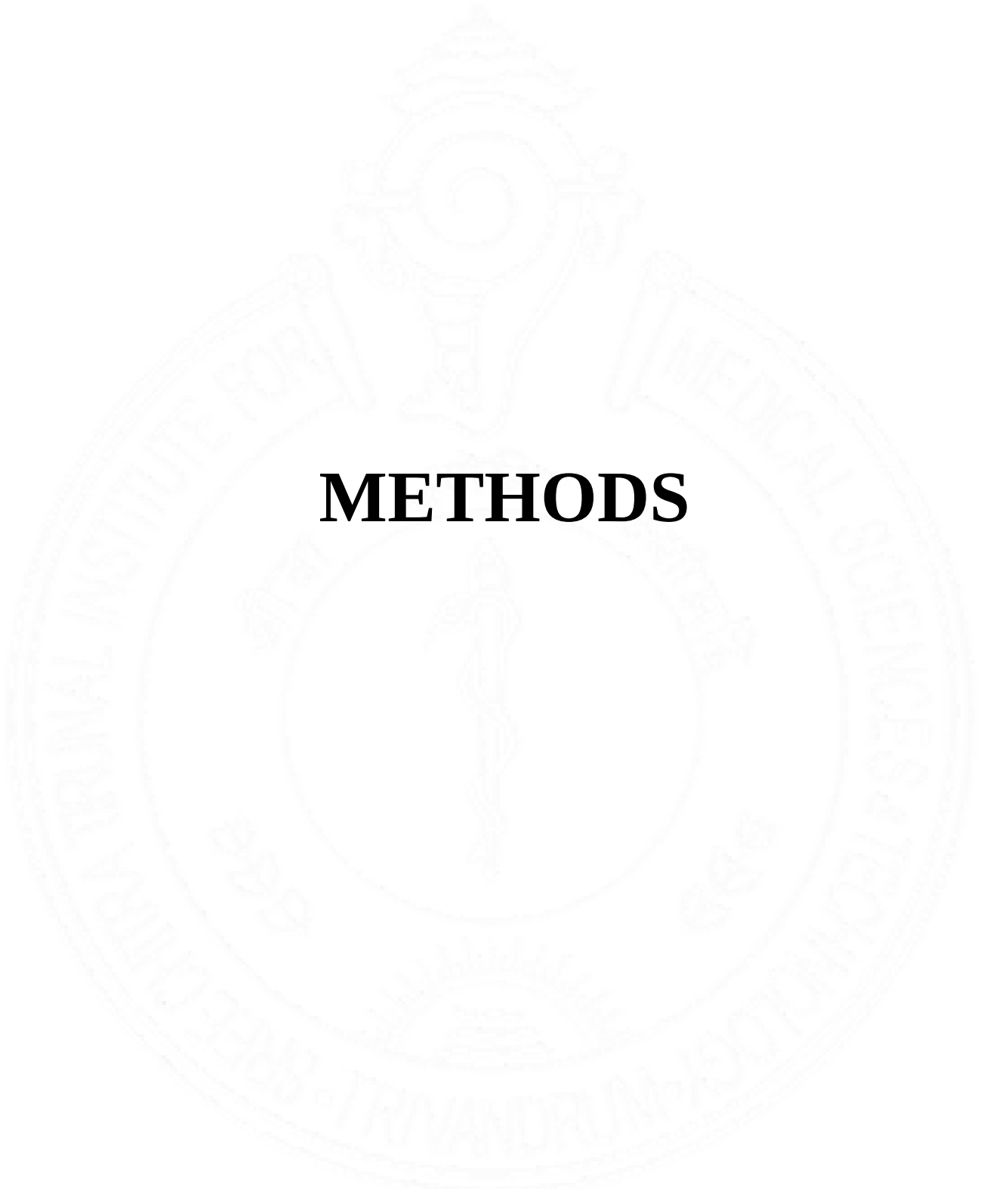
the posterior cortex: a study of 62 cases. Epileptic Disord. 2014 Jun (20)			epileptogenic zone and complete resection predicted favourable surgical outcomes
Shi J, Gao Z, Gao J, et al; Predictors and outcome surgery for posterior cortex epilepsies. Clin Neurol Neurosurg. 2018 Aug; (21)	54	1	59.3% class I outcome; Presence of MRI lesion, concordant ictal and interictal data, no of seizures recorded during pre-surgical monitoring predicted favourable outcome
Davis KL, Murro AM, et al Posterior quadrant epilepsy surgery: predictors of outcome. Seizure. 2012 Nov;21(5)	43	1	51.2% Engel class I outcome; versive head movement unaccompanied by visual aura, non-focal interictal scalp EEG, and pathology other than low grade tumor or cortical dysplasia predicted recurrence
Sarkis RA, Jehi L, et al Seizure outcomes following	63	4.6	64% class I outcome at 1 year; type of resection, preoperative auras, incomplete resection and the

multilobar epilepsy surgery. Epilepsia. 2012 Jan; (22)			presence of postoperative spikes correlated with seizure recurrence
Usui N, et al Posterior cortex epilepsy secondary to ulegyria: is it a surgically remediable syndrome? Epilepsia. 2008 Dec; (23)	10	2	70% Engel class I outcome
Dalmagro CL, et al Clinical features of patients with posterior cortex epilepsies and predictors of surgical outcome. Epilepsia. 2005 (1)	81		65.1% Engel class I outcome; shorter duration of epilepsy and normal neurological examination predicted favourable outcome
Jehi LE, O'Dwyer R, et al A longitudinal study of surgical outcome and its determinants following posterior cortex epilepsy surgery. Epilepsia. 2009 Sep (2)	57	3.3	68.5% Engel class I at 1 year; parietal resections, pathology other than tumor or dysplasia, ipsilateral spiking on EEG, limited resection were poor predictors

Elsharkawy AE, et al ; Long-term outcome of lesional posterior cortical epilepsy surgery in adults. J Neurol Neurosurg Psychiatry. 2009 Jul (16)	80		Predictors of poor outcome- presence of a somatosensory aura, extra regional spikes, incomplete resection, interictal epileptiform discharge (IED) in EEG 6 months and 2 years post surgery, history of GTCS and the presence of focal cortical dysplasia in the resected specimen
Kurwale NS, Patil SB,et al Surgical outcomes for medically refractory epilepsy secondary to posterior cortex ulegyria as sequelae of perinatal insults. Epilepsy Res. 2021 Sep	38	2	75% Engel class I outcome

AIMS AND OBJECTIVES

1. To study the seizure outcomes and predictors in patients undergoing surgery for posterior cortex epilepsy
2. To elucidate the various pathological substrates and study their role in predicting the surgical outcomes
3. To study the various post operative complications and their prevalence



METHODS

STUDY DESIGN AND PATIENT SELECTION:

This study has been carried out at R Madhavan Nayar centre for comprehensive epilepsy care, Department of Neurology, Sree Chitra Tirunal Institute for medical sciences and technology.

It was carried out as a retrospective review of patients who underwent curative surgery for a drug refractory posterior cortex epilepsy between 2000 and 2019, identified from a prospectively maintained registry at our centre. Being a retrospective review, need for a consent was waived by the Institutional Ethics committee. Patients were included in the study based on the following inclusion and exclusion criteria

Inclusion criteria:

1. Patients who underwent curative/ resective posterior cortex surgery
2. Surgery involving either occipital, parietal, or posterior temporal lobes, either alone or in combination or a multi lobar resection/ quadrantectomy
3. Patients with a follow up of at least 1 year post-surgery

Exclusion criteria:

1. Patients with follow up of less than 1 year

2. Patients who underwent palliative procedures like disconnection surgery/
vagal nerve stimulation or callosotomy
3. Patients without adequate clinical details, presurgical evaluation data

Recruitment and data collection procedures: Patients satisfying the inclusion criteria were retrospectively recruited from a prospectively maintained epilepsy database of R Madhavan Nayar centre for comprehensive epilepsy care. Data collected includes basic demographics, clinical details like seizure semiology, frequency, MRI and VEEG data, invasive and electrocorticography , post operative outcomes and post operative follow up details including EEG, MRI , post operative complications and long term follow up details.

Clinical evaluation:

A detailed history was taken from these patients including the age at onset, duration of epilepsy, age at surgery, median seizure score in the year prior to surgery which was assigned as

(0= sz free, off AED; 1= sz free, need of AED uncertain; 2= sz free, need AED;

3= auras only

4= non disabling nocturnal sz only; 5= 1-3/year; 6= 4-11/year; 7= 1-3/month;

8= 1-6/ week

9= 1-3/day; 10= 4-10/day; 11= > 10/day; 12= status without barbiturate coma)

seizure types as defined by ILAE 2017, number of ASM prior to surgery, initial precipitating illness and preoperative examination findings (presence of any visual field defect, limb weakness- hemi or mono paresis), lobes involved.

Presurgical evaluation and selection of surgical candidates: Patients with refractory posterior cortex epilepsy i.e, inadequate control despite use of two optimal medications at appropriate doses underwent prolonged video EEG (VEEG) for recording of events as a part of presurgical evaluation.

Presurgical VEEG evaluation ranged from 1-7 days till adequate number of seizures were recorded to appropriately delineate the epileptogenic zone. A minimum of 2 clinical events were recorded for each of these patients and in case of asymmetric bilateral pathology, a minimum of 6- 8 events were recorded to ascertain laterality. Electrophysiological data was analysed mainly under two domains- interictal and ictal. Interictal epileptiform discharges (IED) were classified as- i) lateralised, localised and confined to the lesion; ii) not confined to , but lateralised and localised; iii) multifocal; iv) completely outside the lesion; v) absence of IED. These were in turn grouped into concordant (i and ii) and non-concordant (iii, iv & v) groups for the final analysis. Ictal onset data was classified as- i) lateralised, localised and concordant to lesion; ii) lateralised or localised only; iii) diffuse onset; iv) uncertain onset. This was then

further grouped into concordant (i and ii) and non concordant (iii and iv) for the final analysis.

A high definition 3T MRI was also done as per Epilepsy protocol including axial and sagittal T2 sequences, coronal high resolution T2, 3D SPGR, FLAIR, SWI, DWI and ASL. The various MRI substrates encountered were studied. The various MRI substrates encountered were gliosis, low grade glioneuronal tumors like ganglioglioma, dysembryoplastic neuroepithelial tumor (DNET), malformations of cortical development- dysplasia, calcified granuloma, vascular malformations like cavernoma, AVM, porencephalic cyst. In those patient with gliosis, a note was made about the presence or absence of Ulegyria on imaging. Following VEEG and MRI, these cases were discussed in Patient management conference (PMC), in the presence of treating neurologist and epileptologist, neuroradiologist and neurosurgeon with regard to surgical feasibility and expected outcomes. A consensus and plan of action was reached at the end of the meet regarding further management plan. Patients were selected for surgery following this meet.

Surgical management: Patients who deemed fit for surgery as per discussion during the patient management conference were planned for elective surgery after detailed discussion with the family regarding pros and cons of surgery, expected seizure outcome and post operative complications. Patients underwent curative resective surgery – lesionectomy, lobectomy, quadrantectomy or multi

lobar resection as decided during the PMC in consultation with neurosurgeon. Patients whose interictal and ictal data was not concordant or those with proximity of eloquent cortex were chosen for invasive monitoring to either identify the epileptogenic zone or map out the resection margin prior to final resective surgery.

Resective surgeries were carried out under the guidance of intra operative electrocorticography (ECoG), where pre and post operative maximum spiking zone was delineated and resection was considered adequate based on the reduction/ absence of spikes on the post operative ECoG. However, in some patients resection was limited due to proximity to eloquent cortex despite high spike load on the post operative ECoG. A note was made of those patients whose resection was limited by proximity to eloquent cortex. Intra operative cortical stimulation and mapping was carried out in patients whose epileptogenic zone was in close proximity to the eloquent area guided by response to stimulation with low and high threshold currents.

Histopathology: Histopathological examination of the substrates was carried out by trained neuropathologists to ascertain the nature of the pathology, with utilisation of special stains wherever deemed necessary

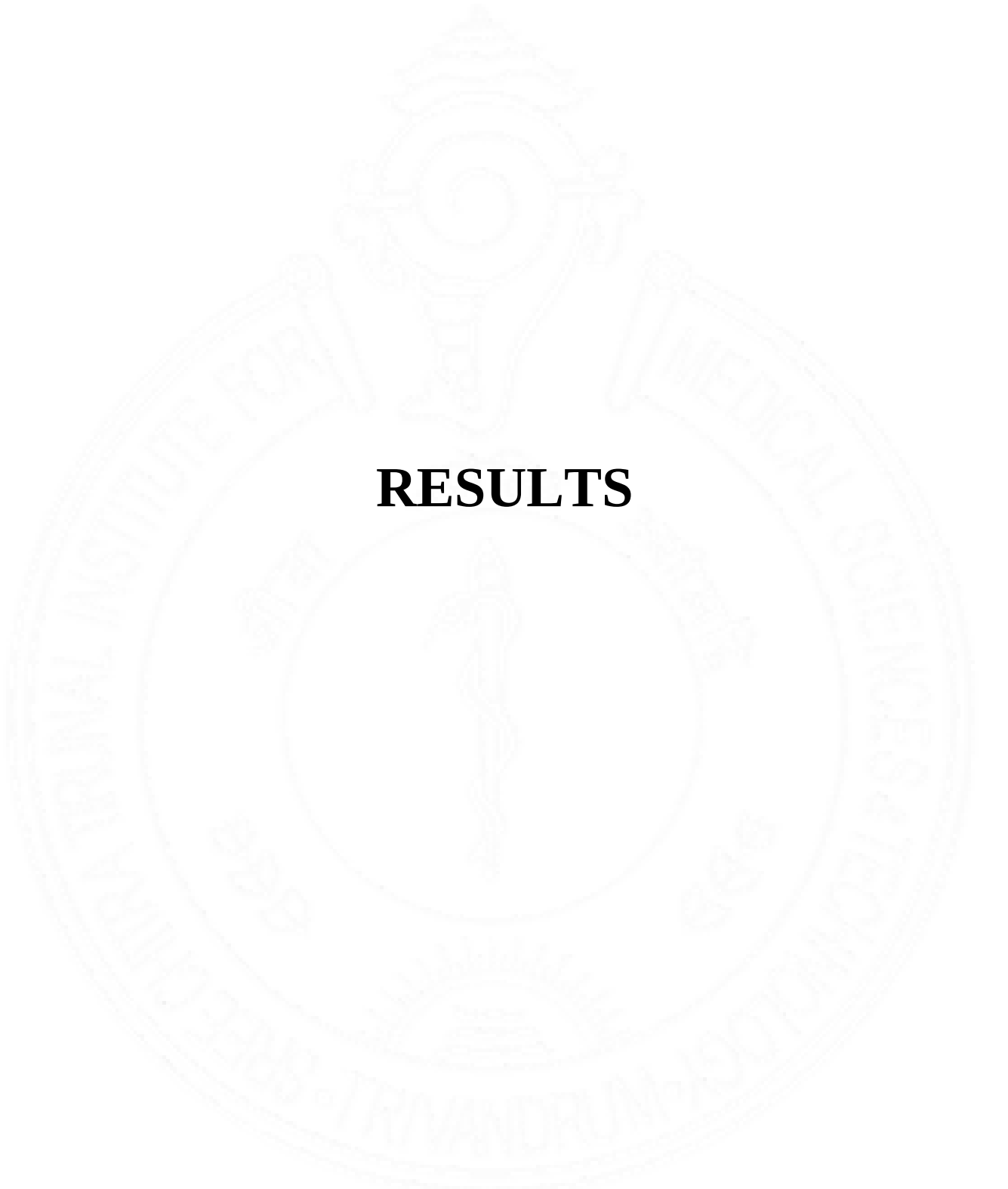
Post operative assessment and follow up: Following surgery patients underwent a scalp EEG on day 7 following suture removal and subsequently at 3months, 1st year , 2nd year and 3rd year post surgery. Patients who had seizures

within the first 2 weeks following surgery were considered to have acute post operative seizures (APOS). Seizure outcome was subsequently ascertained at 3 month, 1 ,2 and 3 year follow up using Engel score. Engel class I and II were considered favourable while class III and IV not favourable. Engel outcome at last follow up since surgery was also assessed. Patients with failed surgery underwent repeat presurgical evaluation and were considered for repeat surgery if feasible and details of the redo surgery were also obtained. Post operative complications were grouped into transient and permanent and their incidence was studied. These included field defects, limb weakness, surgical site infections etc.

Outcome measures:

Seizure outcomes: assessed using Engel score at 3 months, 1 year, 2 year, 3 year post surgery and at last follow up. Engel class I and II were considered favourable while III and IV unfavourable. Predictors of seizure outcome at last follow up were assessed.

Statistical Analysis: All the data was analysed using Microsoft Excel software and SPSS software version 28. Descriptive variables were analysed using descriptive statistics like mean, median and percentages. Seizure outcomes and its predictors were analysed using Mann Whitney U test, chi square test and Fisher exact test as appropriate.



RESULTS

Basic demographics and clinical characteristics:

A total of 191 patients who underwent posterior cortex epilepsy surgery between 2001 and 2019 with a minimum of 1 year follow up post-surgery were included. Mean age at onset of epilepsy was 6 ± 5.3 years. 67.5 % were males (129/191). Mean age at surgery was 17.6 ± 8 years. Mean duration of epilepsy prior to surgery was 11.2 ± 6.9 years. Majority of them had focal seizures along with focal to bilateral tonic clonic seizures (59.7%). A little above one third (36.7%) had focal seizures alone. A small percentage had a combination of multiple seizure types i.e polymorphic including tonic and atonic seizures and these often had an epileptic encephalopathy like presentation. Half of the patients had no obvious initial precipitating illness (54.5%). Birth asphyxia (12.6%) and febrile seizure (11.5%) were the two most common antecedents identified. Definite history of hypoglycemia was identified in only a small percentage (3.1%). Median seizure frequency was 1-6/ week and median number of ASM prior to surgery was 3.

Table 2: Basic demographics and preoperative clinical characteristics

Variable		Number $\pm$ SD (percentage)
		Total n= 191
Age at onset		
Mean		6 ± 5.3 years

median	6
Age at surgery	
Mean SD	17.6±8 years
Median	16
Duration of epilepsy	
Median	10 years
Mean	11.2± 6.849
Sex	
Male	129 (67.5%)
Female	62 (32.5%)
Initial Precipitating Illness	
Birth asphyxia	24 (12.6%)
Febrile seizure	22 (11.5%)
Hypoglycemia	7 (3.7%)
Meningitis/ Encephalitis	13 (6.8%)
Neonatal sepsis	4 (2.1%)
Trauma	4 (2.1%)
Others	10 (5.2%)
None	104 (54.5%)
Seizure types	
Focal seizures alone	70 (36.6%)

Focal and GTCS	114 (59.7%)
Polymorphic	6 (3.1%)
Median seizure frequency score in 1-year prior surgery	8
Median number of ASM at surgery	3

Imaging characteristics:

Gliososis was the most common imaging finding noted in half of the patients (50.3%). Low grade glioneuronal tumors (17.3%) and focal dysplasia (12%) were the other common substrates. Nearly 1/5 th (18%) of the patients with gliosis had Ulegyria on imaging. Other less common substrates encountered were calcified granulomas, porencephalic cyst, cavernoma and leptomeningeal angiomatosis with calcification in cases of Sturge weber syndrome. Dual pathology on MRI was seen in 4/191 patients with secondary mesial temporal sclerosis noted in the same hemisphere.

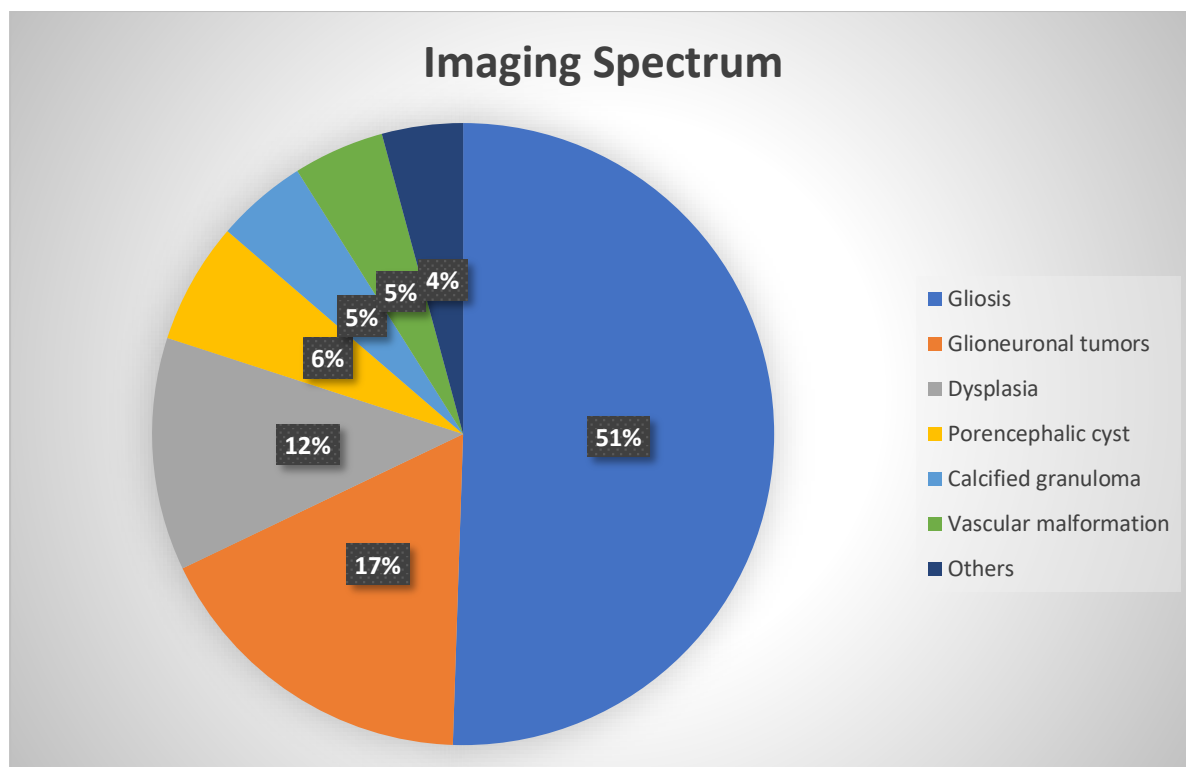


Figure 1 Imaging Spectrum

Histopathological findings: Gliosis remains the most common

histopathological substrate in similar lines that as imaging, occurring in half of the patients (52.3%). Low grade glioneuronal tumors (12.1%), focal cortical dysplasia (10.5%) and low-grade gliomas (8.4%) are the other common substrates. No definite pathology or nonspecific findings identified in a negligible proportion (3/191; 1.5%).

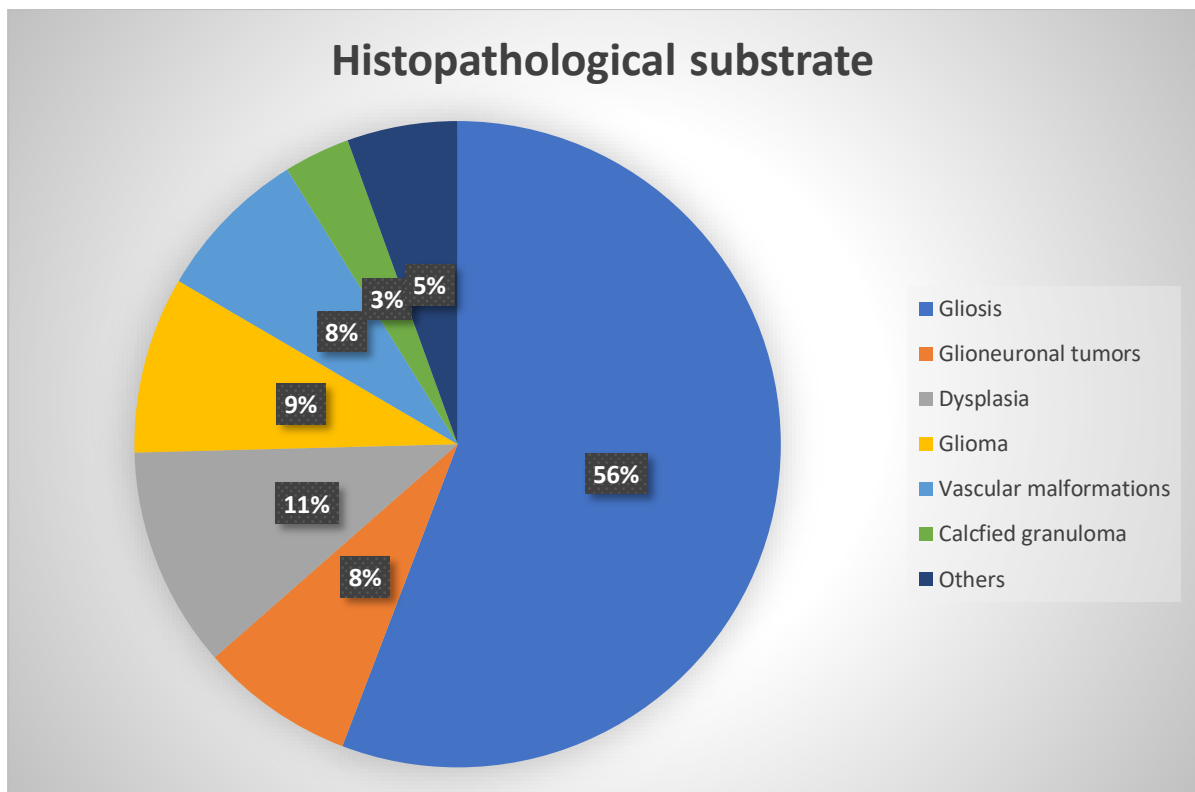


Figure 2 Histopathological substrates

Electrophysiological evaluation:

Scalp VEEG interictal data: Interictal discharges were lateralized, localized and concordant to the lesion in 23.6%. IEDs were not confined to the lesion but concordant in majority (51.3%). Multifocal IEDs (16.9%) and discharges completely outside the lesion (5.2%) area were also encountered in a considerable group. No IEDs were visualized in 3.1% of the patients. Overall $\frac{3}{4}$ th had IEDs concordant to lesion while $\frac{1}{4}$ th had multifocal and non concordant IEDs

Ictal onset was lateralized, localized and concordant in 58.1% while they were either lateralized or localized only in 17.3%. A diffuse onset rhythm was noted in 1/5 th of them (20%), while onset was uncertain in a small fraction (4.7%). Overall, a fairly concordant ictal rhythm was visualized in ¾ th of them while it was diffuse or uncertain in the rest.

Table 3: Electrophysiological parameters

ELECTROPHYSIOLOGICAL PARAMETERS	NUMBER (PERCENTAGE)
INTERICTAL DATA	
Confined to lesion	45 (23.6)
Not confined to lesion but concordant	98 (51.3)
Multifocal	32 (16.9)
Completely outside	10 (5.2)
Absent	6 (3.1)
ICTAL DATA	
Lateralized and localized and concordant	111 (58.1)
Lateralized or localized only	33 (17.3)
Diffuse onset	38 (19.9)

Uncertain onset	9 (4.7)
Invasive monitoring	26 (13.6)

Surgical aspects: Nearly 50% of them underwent lesionectomy, while around 30% underwent lobectomy. A small percentage had to undergo multi lobar resection/quadrantectomy and in around 7%, a concurrent amygdalohippocampectomy was performed due to the presence of a dual pathology. A complete resection could be carried out in 3/4th of them based on ECoG recording. Intraoperative electrocorticography was either not performed nor was found useful due to absence of pre operative spiking in about 1/5th of the patients. In 60% of them, a reduction in postresection spikes was noted, while in 1/5th it was either unchanged or increased.

Table 4: Surgical aspects

TYPE OF SURGERY	NUMBER (%)
Lesionectomy	94 (49.2)
Lobectomy	57 (29.8)
Multilobar resection/ Quadrantectomy	27 (14.1)
Additional surgery- Amygdalohippocampectomy	13 (6.8)

Laterality	
Right	101 (52.9)
Left	90 (47.1)
Degree of resection	
Complete	142 (75.9)
Incomplete	45 (24.1)

Table 5: Intraoperative Electrocorticography (ECoG) details

Intra op ECoG	Number (%)
Pre resection	
Spikes noted	151 (79.1)
Absent spikes	11 (5.8)
Not done	25 (13.1)
Post resection	
Decreased or absent spikes	114 (59.7)
Increased or unchanged	38 (19.9)
Not done	36 (18.8)

OUTCOMES: Seizure freedom from disabling seizures was observed in 63% of the patients with a favorable outcome overall noted in nearly 3/4th of them. Around 10% of the total cohort could be brought off the anti-seizure medications, while the median number of ASM was two in those who continued to use ASM. Redo surgery due to a failed initial surgery was carried out in 7.3% of the patients. Around 28 patients (15.2%) had an Engel class IV outcome and 3 out of these patients were diagnosed with mitochondrial disorders and progressive myoclonic epilepsy syndromes on follow up. A small percentage of these patients with unfavorable outcomes evolved as epileptic encephalopathies of uncertain etiologies.

Table 6: Seizure outcome at last follow up and ASM details

Outcome at last follow up	Number (%)
Engel	
1	116 (63%)
2	19 (10.3%)
3	21 (11.4%)
4	28 (15.2%)
Anti-seizure medication (ASM) details	
Off ASM	17 (9.2%)
Median number of ASM post surgery	2
Redo surgery	14 (7.3%)

Post Operative EEG and MRI details:

Proportion of patient with interictal discharges on postoperative EEG declined significantly after 3 months following surgery and subsequently over the years a consistent declining trend was noted. In contrast, seizure freedom rates dropped steeply in the first 3 months and subsequently remained almost stable over the years. Acute postoperative seizures, i.e within 1 week were noted in 1/5 th of them (41/191, 21%). Post operative MRI was not done in 1/3rd of the patients. 38% had no residual lesion, 27% had a residual lesion while 2% had a contralateral abnormality.

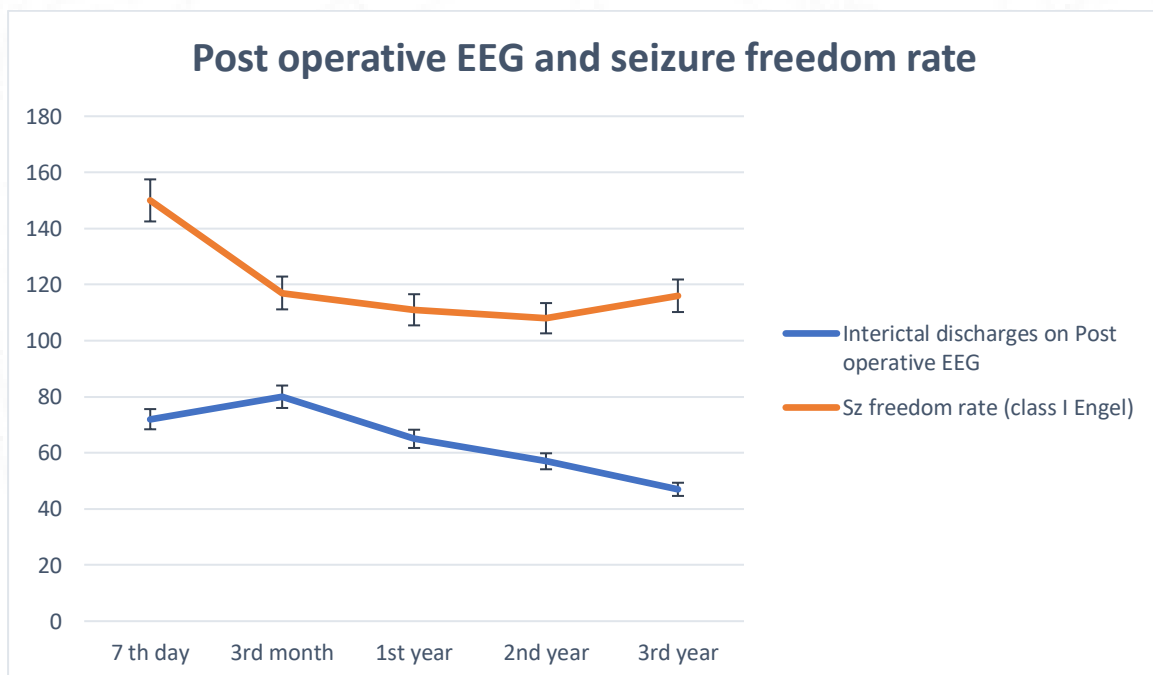


Figure 3 Serial Post operative EEG findings

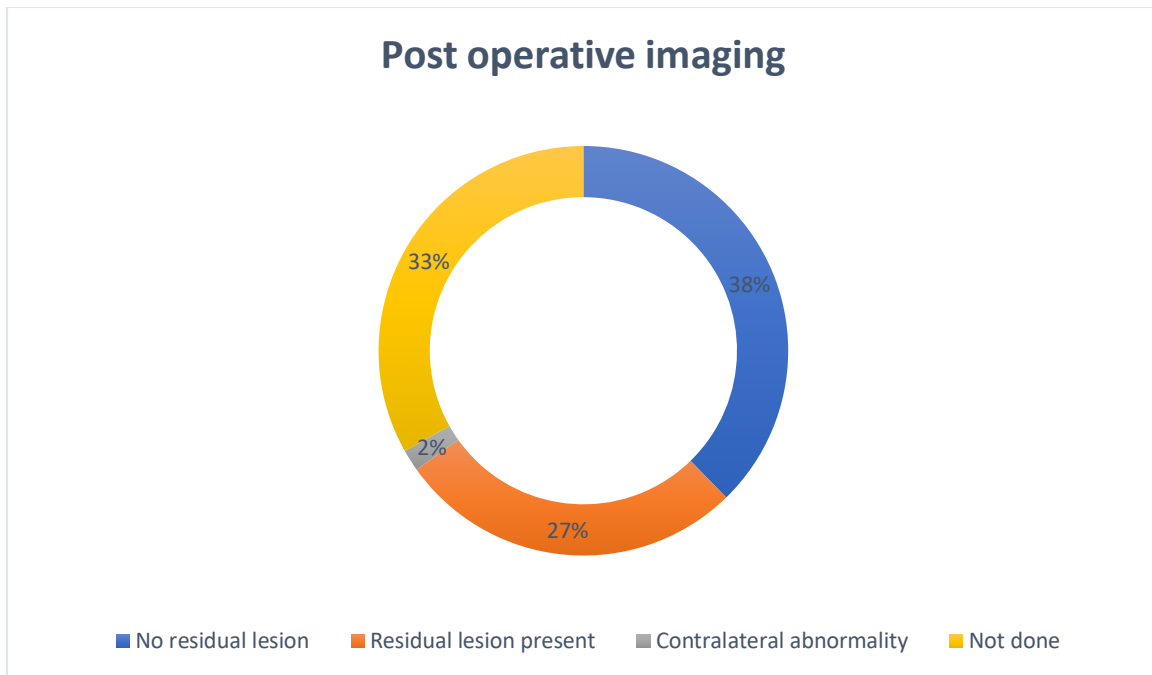


Figure 4 Post operative Imaging

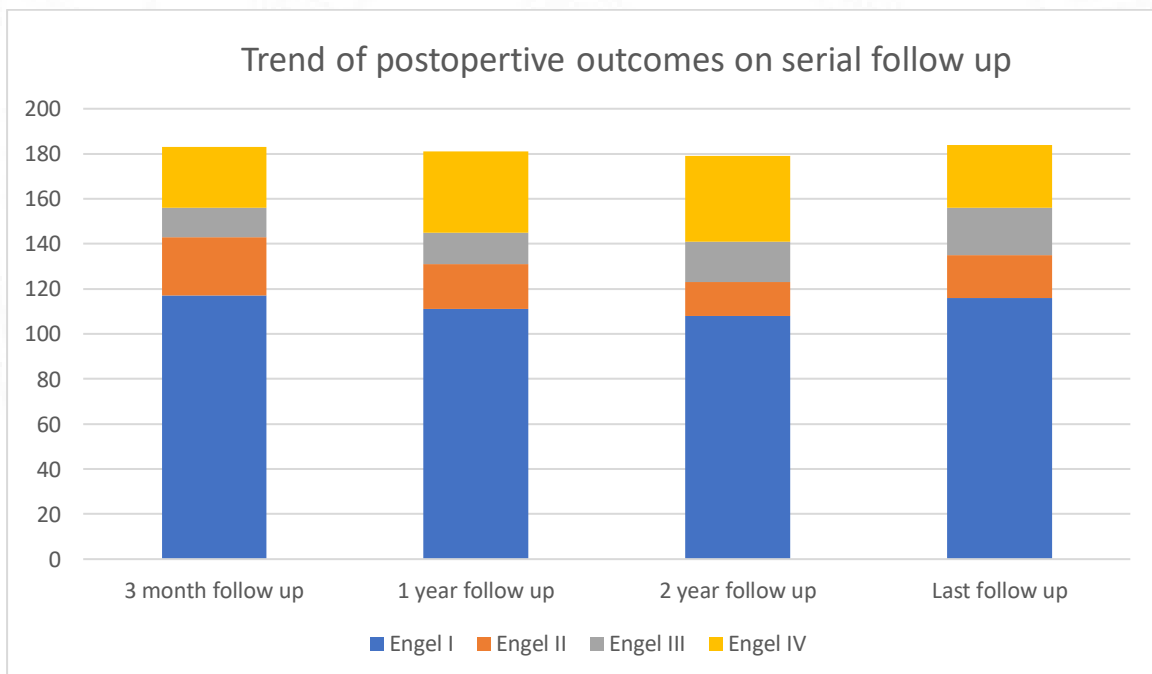


Figure 5 Serial trend in postoperative outcomes on follow up

PREDICTORS OF SEIZURE OUTCOME: Outcome details were available in 184 patients. 7 patients of the total 191 patients in the cohort were excluded, as data on final outcome was not available. On univariate analysis, age at onset < 2 years, <3 median number of ASM prior to surgery, concordant VEEG ictal onset data, complete resection were associated with a favourable outcome. Presence of residual lesion on MRI, acute post operative seizures and IEDs on serial post operative EEG at various intervals following surgery were associated with unfavourable outcome.

On multivariate logistic regression analysis, median number of ASM ($p=0.038$), degree of resection (0.006), acute post operative seizure in first week (0.034), IEDs on post operative EEG at 1 year (0.016) and 2 years (0.076) were considered significant

Table 7: Predictors of outcome at last follow up: bivariate analysis

Variable	Favorable outcome N=135	Unfavorable outcome N= 49	P value
Male sex	91 (74%)	32 (46%)	0.789
Age at onset < 2 years	27 (56.2%)	21 (43.8%)	0.002
Seizure type			
Focal seizure alone	48 (69.6%)	21 (30.4%)	0.359
Focal seizure with GTCS	83 (76.9%)	25 (23.1%)	
Polymorphic	3 (50%)	3 (50%)	
Laterality			
Right	72 (75.8%)	23 (24.2%)	0.443
Left	63 (70.8%)	26 (29.2%)	
MRI Substrate			
Gliosis	66 (71.7%)	26 (28.3%)	0.331
Glioneuronal tumours	28 (84.8%)	5 (15.2%)	
Dysplasia	14 (63.6%)	8 (36.4%)	
Others	27 (73%)	10 (27%)	
Histopathology			
Gliosis	69 (69.7%)	30 (39.3%)	0.139
Glioneuronal tumours	20 (87%)	3 (13%)	
Dysplasia	12 (63.2%)	7 (36.8%)	
Glioma	14 (87.5%)	2 (12.5%)	
<3 (median number) of ASM prior to surgery			
	122 (76.2%)	38 (23.8%)	0.022
VEEG- Interictal data			
Concordant	102 (73.4%)	37 (26.6%)	0.832
Not concordant	33 (75%)	11 (25%)	
VEEG – Ictal onset			
Concordant	110(78.6%)	30 (21.4%)	0.004
Not concordant	25 (56.8%)	19 (43.2%)	
Degree of resection	114 (82%)	25 (18%)	0.000

Acute post op seizure (<1 week)	19 (47.5%)	21 (52.5%)	0.000
Residual lesion on MRI	22 (47.8%)	24 (52.2 %)	0.000
IEDs on post op EEG			
3 month	43 (56.6%)	33 (43.4%)	0.000
1 year	33 (50.8%)	32 (49.2%)	0.000
2 year	33 (57.9%)	24 (42.1%)	0.000
3 year			0.000

Table 8: Predictors on multivariate logistic regression analysis

Variables	Adjusted Odds ratio	95% CI	P value
Median number of ASM before surgery	8.664	0.963-77.935	0.054*
Concordant ictal onset on VEEG	0.477	0.049-4.670	0.525
Age at onset (<2 years)	2.592	0.184-36.524	0.480
Degree of resection	27.515	3.529-214.525	0.002*
Post op MRI	1.350	0.119-15.336	0.809
Acute post operative seizure (<1 week)	7.672	1.286-45.761	0.025*
Post op EEG 1st year	21.362	1.985 - 229.936	.012*
Post op EEG 2nd year	6.326	0.893-44.826	0.065

Complications: Visual field defect was the most common(93%) permanent post operative complication encountered with weakness, sensory loss and aphasia identified in a few. A wide variety of transient complications were noted postoperatively. Weakness was the most common focal deficit while aphasia/ dysphasia and diplopia were found in a small fraction. Post operative delirium (psychosis) was seen in around 1/5th of them. Postoperative meningitis and surgical site infection were the two most common post-surgical complications.

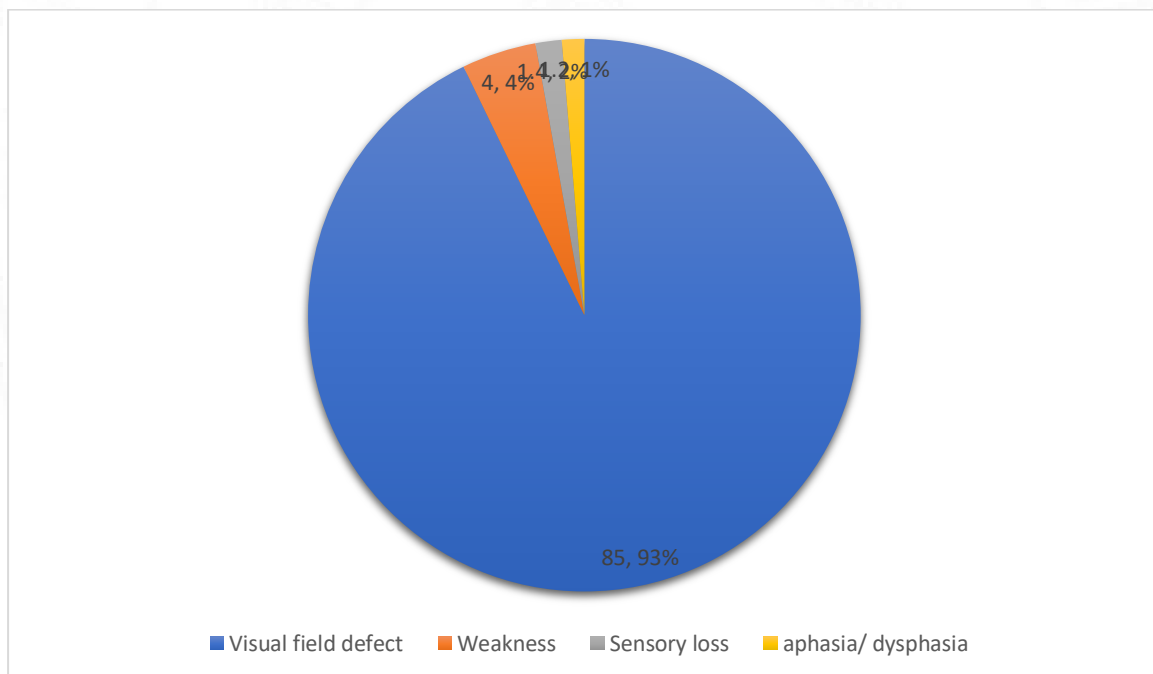


Figure 6 Post operative complications- Permanent

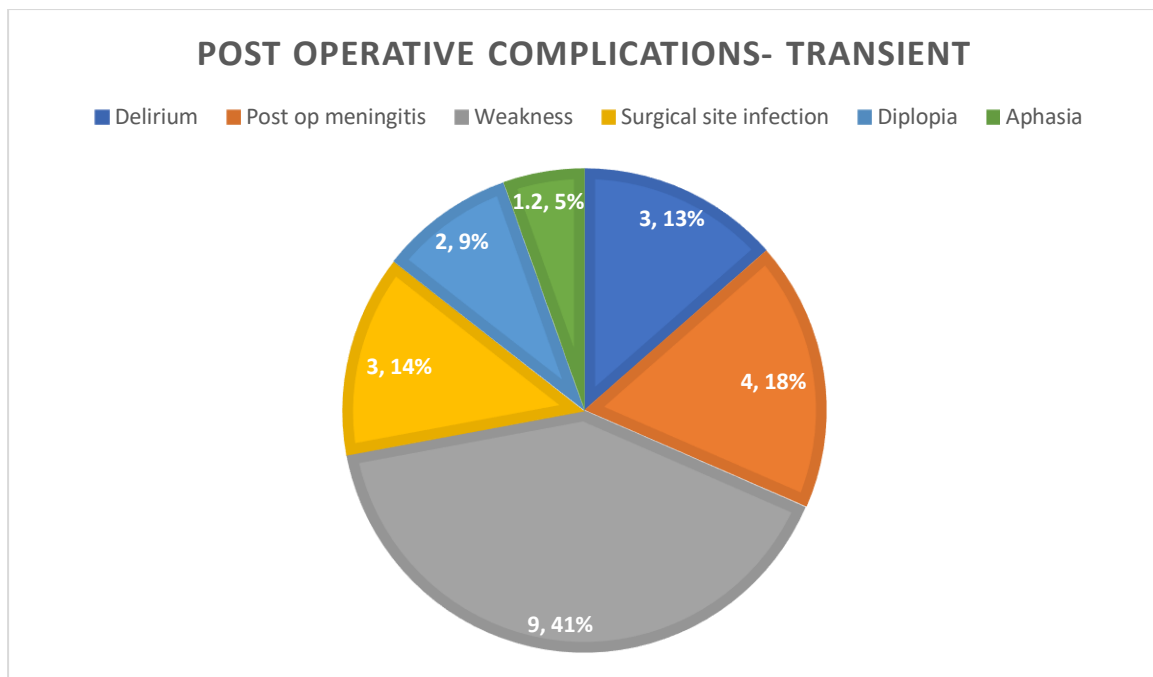


Figure 7 Post operative complications - Transient



DISCUSSION

In this retrospective series carried out on a prospectively maintained cohort of posterior cortex epilepsy patients (n=191), we have explored the various electroclinical characteristics , surgical outcomes and predictors in patients who underwent curative resective surgery. This included patients with either occipital, parietal or posterior temporal involvement either alone or in combination with a minimum 1 year follow up after surgery. This is one of the largest single centre series from the Asian subcontinent which looked at the long term outcomes in PCE surgery with a total sample of 191 patients.

Basic demographic characteristics were in lines with most other studies(15,19,21) with a mean age of onset in the early first decade and a mean duration of epilepsy of nearly 10 years prior to the surgery. No definite initial precipitating illness was obvious in half of the patients in our series despite gliosis being the most common imaging and histopathological substrate. Neonatal hypoglycaemia and hypoxia are the two most common acquired causes of gliosis, especially in developing countries where the perinatal care and awareness about feeding practices are still suboptimal in certain rural areas. Hence, most cases of hypoglycaemia and occult hypoxia may be missed out if not appropriately identified and treated which can result in gliosis that may lead to epileptogenesis after a latent period.

Gliosis is the most common pathology for posterior cortex epilepsy in our series. This is in contrast to the published data from other series (8,15,24) who have a far lower percentage of patients with gliosis as a substrate. Dysplasia and tumours were relatively more common when compared to gliosis unlike our data. This again may be explained by the relatively higher prevalence of perinatal risk factors in low middle income countries.

With respect to the imaging characteristics, studies have found presence of lesion on MRI as an important predictor for good outcome(8,15,19,24) i.e. lesional epilepsy more often fares better when compared to non lesional epilepsy. The latter often requires contribution from other advanced imaging modalities like PET, SPECT and a strong hypothesis for localisation and planning invasive recording as required. These require a sound knowledge and expertise for planning and execution and at the same time, inherently come with a few liabilities compromising on the outcome. In our series, nearly all cases except for one are lesional cases and hence a comparison with this respect is not available. Amongst the various lesions, no difference is found when looked at the outcome with respect to each of these substrates. A small subset of patients had dual pathology with secondary MTS and underwent ATL+ AH in addition to either lesionectomy or lobectomy

Interictal data showed that a significant subset (51.3%) had IEDs outside the lesional area and almost 1/5 th had either multifocal or IEDs exclusively outside the lesional area. This is in contrast to temporal and frontal lobe epilepsy which often have better localised interictal data. This, however did not influence the seizure outcome ($p=0.832$). Ictal rhythm was well localised and lateralised in nearly 60% of the patients with a small fraction showing a rhythm well localised to PHR but bilateral evolution. It is well known that ictal rhythm in cases of occipital lobe pathologies often has a bilateral evolution due to rapid propagation from the mesial occipital region or it can be pseudo lateralised to the opposite side in case of lack of enough tissue to express the rhythm in cases with gliosis or any other underlying pathology. Hence the latter group of patients were also considered to have had concordant data in our study.

Concordant ictal onset was associated with a favourable outcome ($p=0.004$) in contrast to the non-contributory interictal data. Evidence till date in this regard is conflicting with some studies showing concordant interictal data to being more useful (17,21)while others have shown that electrophysiological data neither interictal nor ictal was predictive(15,19,24). Invasive monitoring was required in a small subset to delineate the epileptogenic zone either due to proximity to eloquent cortex or uncertain ictal onset zone. The need for invasive monitoring, has however declined over the years with advances in neuroimaging including the advent of high resolution 3T MRI, PET and SPECT imaging which have essentially eliminated the need for invasive in

many cases. A better understanding and interpretation of the electrophysiological data with the experience gained from the erstwhile invasive recordings has also contributed to the decline in the usage of invasive monitoring especially in lesion cases as a whole. Overall electrophysiological data has an important role in predicting the outcome.

Seizure outcome: At the last follow up , 63% of the patients were free of disabling seizures (Engel class I) and 9% were off ASM. A small fraction (7.3%) underwent redo surgery following a failed initial surgery. Almost 70% had a favourable outcome (Engel class I-II) in similar line of few other large series from across the world. The seizure outcomes within surgical series looking at parietal and occipital lobe lesional epilepsies separately, is around 62% and 65% respectively.(8,24)

Only other study published from India, more than a decade ago with a very small sample size of 19 showed an extremely high seizure freedom rate of more than 90% (17) which was not however observed in our study and neither in any other studies across the world.

The seizure freedom rates have also been assessed in our study at various time points following the surgery i.e at 3 months, 1 year, 2 year and last follow up. Though there was a subtle insignificant decrease in the seizure freedom rate over the years, seizure freedom rates overall have been relatively stable. A new patients have a spontaneous run down in seizure frequency over the years as the epileptogenic network stabilises following surgery while in others evolving epileptogenic networks often cause a run up following a considerable period of remission. A balance between these two phenomena often decides the trajectory of seizure freedom rate over the years. Incomplete resection as decided by the presence of residual lesion on MRI and persisting spikes on intra operative post resection ECoG is one important determinant that has been consistently identified across various studies to predict the outcome. This has been further reiterated in our study.

Predictors of favourable seizure outcome: The various parameters identified to be associated with favourable surgical outcome span across clinical, electrical, radiological and surgical aspects highlighting the contribution of each of these factors and the importance of achieving concordance in various spheres for an optimal surgical outcome. Age of onset above 2 years, less than 3 ASM prior to surgery, concordant preoperative ictal onset data, completeness of resection were associated with a favourable outcome. On the other hand, occurrence of acute post operative seizures within a week of surgery, presence of residual

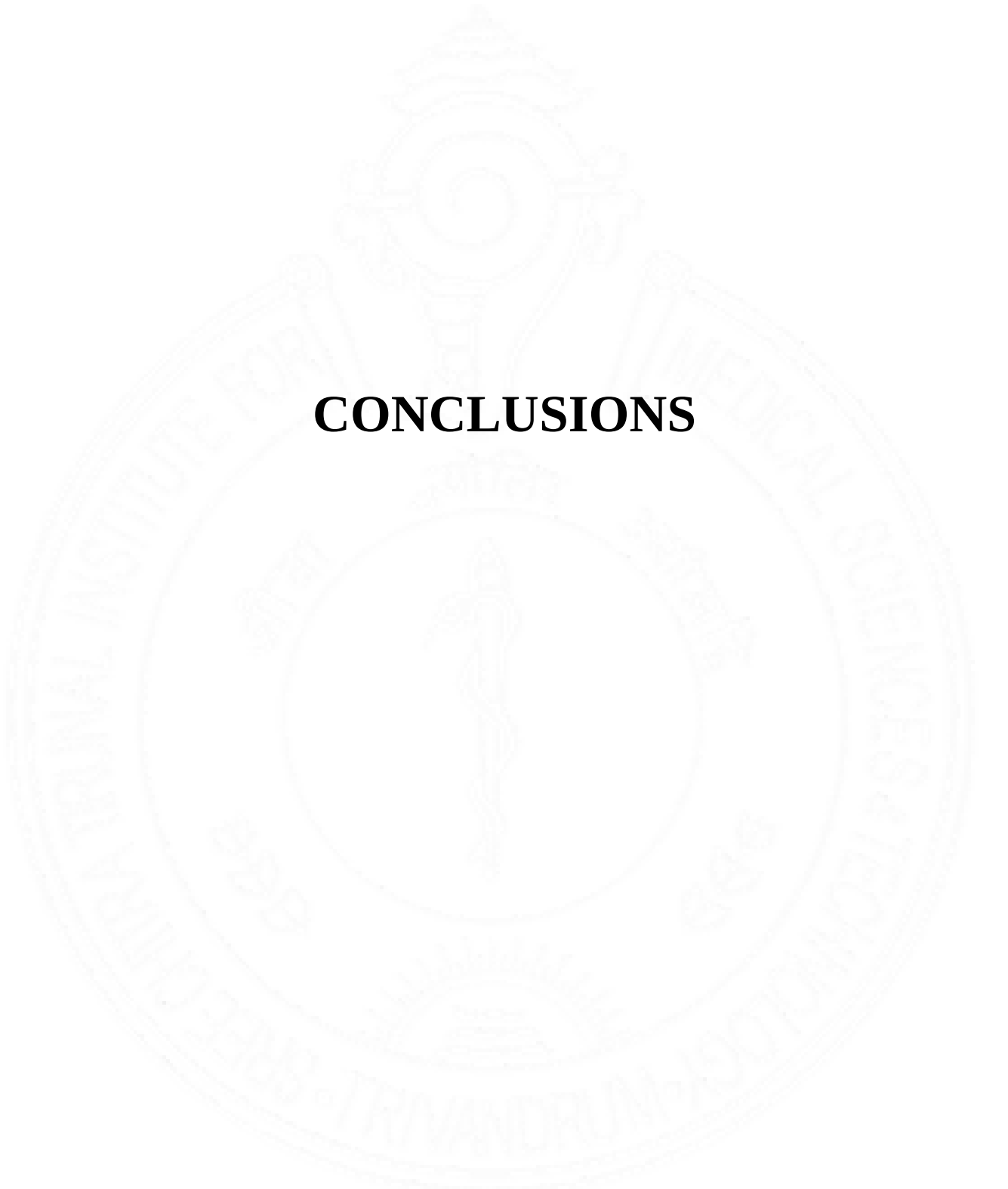
lesion on MRI and IEDs on sequential EEGs were associated with an unfavourable outcome. The various predictors identified in a recently published meta-analysis of posterior cortex surgeries include younger age at onset, abnormal pre op MRI and focal pathology while another met analysis that looked at parietal surgeries alone found concordant interictal EEG data and tumour as the two most important determinants.(8,24)

With regard to post operative complications, our study has meticulously looked into both the transient and permanent complications, not very well elucidated in the earlier studies. Visual decline of varying degrees was the most common complication encountered in more than 90% of which some already had an underlying visual defect. New visual defect was inflicted in around 40% of them with a normal visual field preoperatively. Weakness was the most common transient complication observed followed by post op meningitis and surgical site infection. Most of these complications including weakness improved within a few weeks after the surgery with appropriate measures.

Strengths : One of the largest series of posterior cortex epilepsy surgery patients from the Indian subcontinent. With a mean follow up duration of 12 years , it remains one of the largest series with a long term follow up of more than decade. It also highlights the good follow up rates with very little attrition of our comprehensive epilepsy care centre. A meticulous data collection and analysis

was carried out, backed by a robustly maintained registry. A comprehensive review encompassing all the major aspects including clinical, radiological and electrophysiological parameters was carried out. A detailed review of the post operative complications including permanent and transient was done.

Limitations of our study is that being a retrospective review, inherent constraints with regard to data collection were imminent. Post operative MRI and EEG were not done in a small fraction of patient and details of pre and post operative visual field were also not available in a small fraction. A detailed review of the various clinical auras and their role in predicting the outcome was not done. Neuropsychological evaluation of these patients pre and postoperatively, given the higher order complex activities carried out in this posterior head region and its role in predicting the outcome was not studied. There was some heterogeneity in the review protocol post operatively as it evolved a two decade time period.



CONCLUSIONS

- In this large cohort of patients who underwent curative resective surgery for posterior cortex epilepsy, seizure freedom rate of 63% and an overall favourable outcome of 70% was observed. A small fraction of 9% could come off antiseizure medications
- Gliosis was the most common imaging and histopathological abnormality constituting nearly 50% of all the aetiologies. In contrast, a history of definite perinatal insult was not obvious in about 50% of them
- On univariate analysis, age at onset < 2 years, <3 median number of ASM prior to surgery, concordant VEEG ictal onset data, complete resection were associated with a favourable outcome. Presence of residual lesion on MRI, acute post operative seizures and IEDs on serial post operative EEG at various intervals following surgery were associated with unfavourable outcome
- On multivariate logistic regression analysis, median number of ASM ($p=0.038$), degree of resection (0.006), acute post operative seizure in first week (0.034), IEDs on post operative EEG at 1 year (0.016) and 2 years (0.076) were considered significant
- Visual decline of varying degrees was the most common permanent complication encountered, while weakness, postop meningitis, surgical site infection and delirium were some of the common transient complications.

REFERENCES:

1. Dalmagro CL, Bianchin MM, Velasco TR, Alexandre V, Walz R, Terra-Bustamante VC, et al. Clinical Features of Patients with Posterior Cortex Epilepsies and Predictors of Surgical Outcome. *Epilepsia*. 2005 Sep;46(9):1442–9.
2. Jehi LE, O'Dwyer R, Najm I, Alexopoulos A, Bingaman W. A longitudinal study of surgical outcome and its determinants following posterior cortex epilepsy surgery. *Epilepsia*. 2009 Sep;50(9):2040–52.
3. Barba C, Doglietto F, Luca L, Faraca G, Marra C, Meglio M, et al. Retrospective analysis of variables favouring good surgical outcome in posterior epilepsies. *J Neurol*. 2005 Apr;252(4):465–72.
4. Harward SC, Chen WC, Rolston JD, Haglund MM, Englot DJ. Seizure Outcomes in Occipital Lobe and Posterior Quadrant Epilepsy Surgery: A Systematic Review and Meta-Analysis. *Neurosurgery*. 2018 Mar;82(3):350–8.
5. Davis KL, Murro AM, Park YD, Lee GP, Cohen MJ, Smith JR. Posterior quadrant epilepsy surgery: Predictors of outcome. *Seizure*. 2012 Nov;21(9):722–8.
6. Salanova V, Andermann F, Oliver A, Rasmussen T, Quesney LF. OCCIPITAL LOBE EPILEPSY: ELECTROCLINICAL MANIFESTATIONS, ELECTROCORTICOGRAPHY, CORTICAL STIMULATION AND OUTCOME IN 42 PATIENTS TREATED BETWEEN 1930 AND 1991: SURGERY OF OCCIPITAL LOBE EPILEPSY. *Brain*. 1992;115(6):1655–80.
7. Salanova V, Andermann F, Rasmussen T, Olivier A, Quesney LF. Parietal lobe epilepsy Clinical manifestations and outcome in 82 patients treated surgically between 1929 and 1988. *Brain*. 1995;118(3):607–27.
8. Pilipović-Dragović S, Ristić AJ, Bukumirić Z, Trajković G, Sokić D. Long-term seizure outcome following epilepsy surgery in the parietal lobe: a meta-analysis. *Epileptic Disord*. 2018 Apr;20(2):116–22.
9. Kim DW, Lee SK, Yun CH, Kim KK, Lee DS, Chung CK, et al. Parietal Lobe Epilepsy: The Semiology, Yield of Diagnostic Workup, and Surgical Outcome. *Epilepsia*. 2004 Jun;45(6):641–9.

10. Francione S, Liava A, Mai R, Nobili L, Sartori I, Tassi L, et al. Drug-resistant parietal epilepsy: polymorphic ictal semiology does not preclude good post-surgical outcome. *Epileptic Disord.* 2015 Mar;17(1):32–46.
11. Asadollahi M, Sperling MR, Rabiei AH, Asadi-Pooya AA. Drug-resistant parietal lobe epilepsy: clinical manifestations and surgery outcome. *Epileptic Disord.* 2017 Mar;19(1):35–9.
12. Binder DK, Podlogar M, Clusmann H, Bien C, Urbach H, Schramm J, et al. Surgical treatment of parietal lobe epilepsy: Clinical article. *J Neurosurg.* 2009 Jun;110(6):1170–8.
13. Cascino GD, Hulihan JF, Sharbrough FW, Kelly PJ. Parietal Lobe Lesional Epilepsy: Electroclinical Correlation and Operative Outcome. *Epilepsia.* 1993 May;34(3):522–7.
14. Harroud A, Boucher O, Tran TPY, Harris L, Hall J, Dubeau F, et al. Precuneal epilepsy: Clinical features and surgical outcome. *Epilepsy Behav.* 2017 Aug;73:77–82.
15. Jehi LE, O'Dwyer R, Najm I, Alexopoulos A, Bingaman W. A longitudinal study of surgical outcome and its determinants following posterior cortex epilepsy surgery. *Epilepsia.* 2009 Sep;50(9):2040–52.
16. Elsharkawy AE, El-Ghandour NMF, Oppel F, Pannek H, Schulz R, Hoppe M, et al. Long-term outcome of lesional posterior cortical epilepsy surgery in adults. *J Neurol Neurosurg Psychiatry.* 2009 Jul 1;80(7):773–80.
17. Daniel RT, Meagher-Villemure K, Farmer JP, Andermann F, Villemure JG. Posterior Quadrantic Epilepsy Surgery: Technical Variants, Surgical Anatomy, and Case Series: POSTERIOR QUADRANTIC EPILEPSY SURGERY. *Epilepsia.* 2007 Apr 18;48(8):1429–37.
18. Ramantani G, Stathi A, Brandt A, Strobl K, Schubert-Bast S, Wiegand G, et al. Posterior cortex epilepsy surgery in childhood and adolescence: Predictors of long-term seizure outcome. *Epilepsia.* 2017 Mar;58(3):412–9.
19. Liava A, Mai R, Cardinale F, Tassi L, Casaceli G, Gozzo F, et al. Epilepsy surgery in the posterior part of the brain. *Epilepsy Behav.* 2016 Nov;64:273–82.
20. Liava A, Mai R, Tassi L, Cossu M, Sartori I, Nobili L, et al. Paediatric epilepsy surgery in the posterior cortex: a study of 62 cases. *Epileptic Disord.* 2014 Jun;16(2):141–73.

21. Shi J, Gao Z, Gao J, Li G, Chen Y. Predictors and outcome surgery for posterior cortex epilepsies. *Clin Neurol Neurosurg*. 2018 Aug;171:124–8.
22. Sarkis RA, Jehi L, Najm IM, Kotagal P, Bingaman WE. Seizure outcomes following multilobar epilepsy surgery: Multilobar Epilepsy Surgery. *Epilepsia*. 2012 Jan;53(1):44–50.
23. Usui N, Mihara T, Baba K, Matsuda K, Tottori T, Umeoka S, et al. Posterior cortex epilepsy secondary to ulegyria: Is it a surgically remediable syndrome? *Epilepsia*. 2008 Dec;49(12):1998–2007.
24. Harward SC, Chen WC, Rolston JD, Haglund MM, Englot DJ. Seizure Outcomes in Occipital Lobe and Posterior Quadrant Epilepsy Surgery: A Systematic Review and Meta-Analysis. *Neurosurgery*. 2018 Mar;82(3):350–8.

KEYWORDS AND ABBREVIATIONS

EEG- Electroencephalogram

VEEG- Video electroencephalogram

MRI- Magnetic resonance imaging

PCE- Posterior cortex epilepsy

ASM- Anti seizure medication

FCD – focal cortical dysplasia

DNET- Dysembryoplastic neuroepithelial tumor

IED- Interictal discharges

PHR- posterior head region

TPO- temporo parieto occipital

PET- Positron emission tomography

SPECT- Single photon emission computerized tomography

PROJECT PROFORMA

1. Master file number
2. Age
3. Sex
4. Age at onset of habitual seizures:
5. Date of surgery
6. Type of surgery
7. Initial Precipitating Injury-
 - a) Hypoxia
 - b) Hypoglycemia
 - c) Encephalitis/Meningitis
 - d) Febrile status
 - e) Head trauma
 - f) others- specify
 - g) None
8. Seizure type:
 - a. Focal awareness preserved seizure
 - b. Focal awareness impaired seizure
 - c. Focal to bilateral tonic clonic seizure
 - d. focal+ bilateral tonic clonic seizure
 - e. Atonic drops
 - f. Myoclonic
 - g. Absence
 - h. Tonic
9. Duration of epilepsy:
10. Frequency of seizures in the preceding 12 months:
11. Status Epilepticus: Yes(Y)=1/No(N)=0
12. 2 years of remission of seizures anytime: Y=1/N=0
13. Lobe/s involved: Frontal (F), Parietal (P), Temporal (T), Occipital (O) ,
Multilobar (ML, specify the lobes involved)
14. No. of ASMs at surgery:
15. Invasive done/not (Y=1/N=0); If yes, reason
 - a. Ictal onset zone
 - b. Eloquent area
 - c. 1+2 (Ictal onset zone + Eloquent area)
 - d. Normal MRI
 - e. Others

16. WADA done/not (Y=1/N=0), If yes, 2-right, 3-left

17. fMRI (Y=1/N=0), If yes, 2-right, 3-left

18. MRI—substrate

- a. Gliosis
- b. Ganglioglioma
- c. DNET
- d. FCD
- e. Normal
- f. Ulegyria
- g. Others-specify

19. HPE:

- a. Gliosis
- b. Porencephalic cyst
- c. Cortical cyst
- d. AVM
- e. Cavernous angioma
- f. FCD
- g. Others-specify

20. Interictal data

A= confined to lesional area (F, P, T, O, MF)

B= Not confined

C= Completely outside

D= No IEDs

21. Ictal onset:

Concordant= 1; discordant =2; diffuse onset=3

22. Invasive: (1-frontal, 2-parietal, 3-occipital, 4-temporal)

Irritative zone (IEDs)

Ictal zone zone

Cortical surface mapping-eloquent 0- Not done

- 1. Yes- encroaching the lesion
- 2. No-not encroaching eloquent region

23. Degree of resection:

- 1. complete
- 2. incomplete

h. meningitis

33. Engel score (class):

I. Free of disabling seizures

II. Rare disabling seizures (almost seizure free)

III. Worthwhile improvement

IV. No worthwhile improvement

34. Date of last follow up:

IEC APPROVAL

 श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
Thiruvananthapuram - 695 011, Kerala, India
(An Institute of National Importance under Govt. of India)
Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

Institutional Ethics Committee
(IEC Regn No. ECR/189/Inst/KL/2013/RR-21)

SCT/IEC/1905/AUGUST/2022 22.12.2022

Dr. Harini Pavuluri
Post Doctoral Fellow
Department of Neurology
SCTIMST, Thiruvananthapuram

Dear Dr. Harini Pavuluri,

The Institutional Ethics Committee held on 6th August, 2022, reviewed and discussed your application to conduct the study titled "LONG TERM SURGICAL OUTCOMES AND PREDICTORS IN POSTERIOR CORTEX EPILEPSY" (IEC/1905).

The following members of the Ethics Sub-committee were present at the meeting held on 6th August, 2022.

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Prof. Kala Kesavan P	MBBS,MD	Female	Basic Medical Scientist	No
2.	Dr. Pradeep S	MBBS, MD	Male	Basic Medical Scientist	No
3.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
4.	Dr. Christina George	MD Psychiatry	Female	Clinician	No
5.	Adv. N Anand	BAL, L.LB	Male	Legal Expert	No
6.	Dr. Rejnish Kumar	MBBS,MD ,DNB	Male	Clinician	No
7.	Prof. Narayanan Namboodiri. K K	MBBS,MD,DM	Male	Clinician	Yes
8.	Dr. Srinivas G	PhD	Male	Basic Medical Scientist (Member Secretary)	Yes

Page 1 of 2

The following documents were reviewed:

SCT/IEC/1905/AUGUST/2022

Original submission

1. Checklist Form
2. Covering letter addressed to the Chairman, IEC, SCTIMST
3. IEC Application Form
4. Declaration form
5. Project Proposal
6. CV of PI and Co-PI
7. Proforma
8. SRC Recommendation letter

Revised submission

1. Covering letter addressed to the Chairman, IEC, SCTIMST
2. Response to IEC recommendations
3. Checklist Form
4. Forwarding letter from HOD
5. IEC Application Form
6. Declaration form
7. Project Proposal
8. CV of PI and Co-PI
9. Proforma

IEC Decision

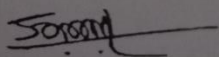
The IEC approved the conduct of the study in the present form.

Remarks:

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

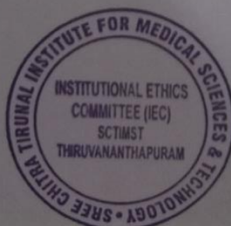
There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,



Dr. G. Srinivas
Member Secretary, IEC

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST, THIRUVANANTHAPURAM





Plagiarism Checker X - Report

Originality Assessment

Overall Similarity: **2%**

Date: Dec 28, 2022

Statistics: 117 words Plagiarized / 6018 Total words

Remarks: Low similarity detected, check your supervisor if changes are required.

v 7.0.10 - WML 3
FILE - PDF THESIS (1).DOCX