UTILITY OF INTRA-OPERATIVE ELECTROCORTICOGRAPHY (ECOG) FOR LESIONAL EPILEPSY: A RANDOMISED CONTROLLED TRIAL

(IO-ECOG TRIAL)

Dr. SREENATH P R

MCh NEUROSURGERY THESIS

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A THESIS SUBMITTED BY

Dr SREENATH P R

TO

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM.

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE AWARD OF

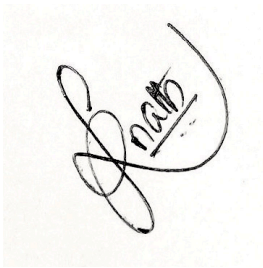
MCH NEUROSURGERY

2022

DECLARATION BY THE STUDENT

CERTIFICATE

I, Dr Sreenath P R hereby certify that I had personally carried out the work depicted in the thesis titled, “UTILITY OF INTRA-OPERATIVE ELECTROCORTICOGRAPHY (ECOG) FOR LESIONAL EPILEPSY: A RANDOMISED CONTROLLED TRIAL (IO-ECOG TRIAL)”, No part of this thesis has been submitted for the award of any other degree or diploma prior to this date.b



Dr Sreenath P R

27 July 2022

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*Clearance was obtained from the Institutional Ethics Committee and Clinical Trial Registry of India (CTRI) for carrying out the study.

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LIST OF ABBREVIATIONS

S	Abbreviation	Full Form
1	ECoG	Electrocorticography
2	LEATs	Long Term Epilepsy Associated Tumors
3	ASM	Anti-Seizure Medication
4	ILAE	International league against epilepsy
5	LMIC	Low-middle income countries
6	LIC	Low income countries
7	fMRI	functional MRI
8	PLNTY	Polymorphous low-grade neuroepithelial tumor of the
9	DNET	Dysembryoplastic neuroepithelial tumor
10	SD	Standard deviation
11	MRI	Magnetic resonance imaging
12	MAC	Minimum alveolar concentration

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APPROVAL OF THE THESIS

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SYNOPSIS

UTILITY OF INTRA-OPERATIVE ELECTROCORTICOGRAPHY (ECOG) FOR LESIONAL EPILEPSY: A RANDOMISED CONTROLLED TRIAL

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SYNOPSIS

Background

About 25-30% of patients with epilepsy are drug resistant and need a pre-surgical work up to assess surgical candidacy. Though used routinely in specialised epilepsy centers, Electrocorticography (ECoG) usage is not clearly established. Robust evidence doesnot exist to support its regular usage in Long term Epilepsy associated tumors (LEATs) which constitutes approximately 25-35% cases of drug resistant epilepsy.

Objectives

We aimed to evaluate if acute intra-operative ECoG is useful in LEATs with the objective of developing standardized protocols and practice parameters. Using a randomized study design, we sought to generate Class I evidence to address this research question.

Methods

Prospective randomized study, including all patients operated for drug resistant epilepsy with non-eloquent area LEATs at our tertiary comprehensive care center. Patients were randomized into 2 groups namely Group I (without usage of ECoG) and Group II (with ECoG usage). Group II patients further underwent tailored resections if necessary, as per ECoG practice protocols. Surgical outcomes were evaluated for seizure outcome (Engel scale) and adverse event profile.

Results

Total of 42 patients operated for LEATs having drug resistant epilepsy were included in the study with mean age of 22 years (SD 12) with 60% patients having temporal lesions and 17 patients with extratemporal lesions. 19 patients belonged to Group I and 23 patients belonged to Group II with mean follow-up period of 15.68 and 13.21 months respectively. 26% patients (n=6) in Group II underwent extended resection based on rhythmic persistent post resection spikes. 100% of Group II patients had Engel score I during follow up compared to 94% of Group I with Engel score I (p= 0.700).

Conclusions

Though ECoGs role may have been established in focal cortical dysplasia, its utility in LEATs is limited. Our randomized study confirmed that there is no added benefit conferred using ECoG in LEATs. Additional tailored resections aided by ECoG also did not yield seizure outcome benefits in LEATs.

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Dr Sreenath P R

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INTRODUCTION

About 25-30 % of patients with epilepsy are medically refractory and need a pre-surgical work up to assess surgical candidacy. After a detailed pre surgical work up, as per standard protocols, surgical resections for epilepsy are planned. The aims of epilepsy surgery are to cure seizures, limit anticonvulsants, avoid unexpected neurological deficits and improve overall quality of life[1-3].

About 50 million people suffer from epilepsy, of whom 80% live in resource poor countries. A gross imbalance exists in the availability of epilepsy surgery services with its availability restricted to about 13-21 % of LMIC and nearly 66% of HIC. Menon and Radhakrishnan report that only one in 1000 deserving patients receive epilepsy surgery in India[2].

During surgical resections for epilepsy, acute intra-operative electrocorticography (ECoG) is used to record electrical activity from the surgically exposed cortical surface. It is proposed to have additional utility in guiding the extent of surgical resection of the 'ictal onset zone'. Use of EcoG in patients with structural lesions like LEATS (Long-term epilepsy associated tumors) remains less explored[3]. This study therefore aims to develop Class 1 evidence to evaluate the utility of ECoG in lesional epilepsy.

Electrocorticography (ECoG) is a neurophysiological technique used to record cortical potentials from the exposed brain in the operating room. It is used in the surgical treatment of people with medically refractory epilepsy. ECoG finds its importance in confirming and outlining the actual site and extent of the

epileptogenic process prior to resection. It is also used to determine if all the potentially epileptogenic tissue has been removed in epilepsy surgery. Use of ECoG in patients in whom structural lesions have been identified on imaging studies remains less explored and sometimes controversial.

The removal of the ‘‘epileptogenic zone’’ consisting of the lesion and a surrounding critical mass of tissue is required for a successful surgical outcome[3]. ECoG has been reported to provide useful information for the localisation of this area at the time of surgery. While there have been several publications related to ECoG, most of them have been case reports or series without a proper control group. Hence the role of the technique has been questioned. The use of ECoG in patients with structural lesions on imaging studies remains one of its best used indications albeit being controversial. Comparison between ECoG guided resections and non-ECoG guided resection for similar groups of lesions have not been prospectively done.

AIMS AND OBJECTIVES

The aims of the study are as follows.

1. To evaluate if acute intra operative ECoG is useful in Long term epilepsy associated tumors (LEATs) .

2. To develop standardised protocols for intra operative ECoG in Long term epilepsy associated tumors.

3.To develop intra operative ECoG scoring systems for planning tailored resection strategies

REVIEW OF LITERATURE

LONG-TERM EPILEPSY ASSOCIATED TUMORS (LEATs)

Brain tumors are associated with epilepsy in more than a 50% of cases (mostly low grade tumors) and approximately 30% of these tumor-associated epilepsy are observed to be pharmaco-resistant. The idea of long-term epilepsy associated tumors (LEAT) was introduced to describe the wide group of low grade tumors associated with chronic epilepsy in these patients[1-5].

In the spectrum of epilepsy surgery, tumors of the brain are the second most common cause of chronic epilepsy[6] and it could be encountered in an average 30% of patients operated on for refractory epilepsy[5,7,8].

The term long-term epilepsy-associated tumors (LEAT) was introduced in 2003 considering the fact that some patients with drug-resistant seizures episodes for 2 or more years had brain tumors diagnosed clinically or on imaging which were different from diffuse gliomas[5]. Although any tumor type involving the brain could cause seizures, LEATs are considered as an entity of its own clearly to be identified on MRI.

Epidemiology of LEAT

Every fourth patient with chronic pharmaco-resistant epilepsy who undergoes epilepsy surgery is diagnosed with an intra-axial brain tumor[8]. Clinically and pathologically two cohorts can be identified. The first group (LEAT) is histologically in most cases glioneuronal tumors consisting of both neuronal and glial elements. Within this group, gangliogliomas (around 10%) and

dysembryoplastic neuroepithelial tumors (DNETs) (around 6%) account for the majority; they represent the second most common cause in adults and the third most common cause in children undergoing epilepsy surgery[9]. The second group histologically consists mainly of diffuse gliomas, namely (IDH1/2-mutated) astrocytomas, oligodendrogliomas, and the occasional anaplastic cases[5,10]. Few purely neuronal tumors like multinodular and vacuolating neuronal tumor of cerebrum, mixed tumors like glioneuronal tumor with neuropil islands, or purely glial tumors like pilocytic astrocytoma, pleomorphic xanthoastrocytoma and cortical ependymomas do not perfectly fit into this categorization.

Pathophysiology

Glioneuronal tumors are found to cause focal and/ or secondarily generalized seizures due to their location in the cortex. Seizure control with antiepileptic drugs are often not sufficient.

Ganglioglioma

Ganglioglioma is a slow growing well-differentiated glioneuronal tumor consisting of dysplastic ganglion cells and neoplastic glial cells. They are often found to arise in the temporal lobe in association with seizures. However, they can also occur at any age and anywhere throughout the neuraxis including the cerebellum, brainstem, and spinal cord. They often display a mix of solid and cystic components on histology. Most gangliogliomas histologically belong to WHO grade I and seldom recur after complete resection. However, gangliogliomas could be both

histologically and clinically variable, and the tumor recurrence or anaplastic progression can occur in a subset of patients[11].

Imaging usually reveals the tumor location in the cortex or in the cortex and subcortical white matter interface with a preference for parahippocampal and lateral temporo-occipital gyri. The typical imaging features are a combination of intracortical cysts, circumscribed areas of cortical and subcortical signal changes on FLAIR and T2 images, and nodular contrast enhancement. Calcifications are noted in around one third of the cases and contrast enhancement in approximately 50% of cases.

On pathological and molecular studies, Glioneuronal tumors are noted to consist of dysplastic neurons and neoplastic glial cells with the spectra ranging from predominantly neuronal type to predominant glial cells. Immunohistochemically, CD34 expression is noted in majority of the tumor profiles. Cortical dysplasia is a common association with gangliogliomas. V600E mutation in the BRAF gene has been found in 25% of gangliogliomas[10].

Approximately, 95% of gangliogliomas are profiled to be WHO grade I and 5% as WHO grade III tumors[12]. Overall recurrence is noted in the range of around 7% but distinctly larger for grade III tumors. Extratemporal location of the tumor, male sex, age at surgery > 40 years, a history without seizures, incomplete surgical resection, and presence of a gemistocytic cell components on histology are factors that bestow poor prognosis in these cases.

Dysembryoplastic Neuroepithelial Tumor (DNET)

Dysembryoplastic neuroepithelial tumor (DNET) is a mixed neuronal-glial neoplasm belonging to WHO Grade I tumors, described first by Daumas-Duport in 1988, causing early onset of epilepsy in children and young adults.

The relative rarity of these tumors, lack of pathognomonic clinical and radiological findings and resemblance with other intra-axial tumors of young make their diagnosis difficult from a clinico-radiological standpoint and also histopathologically. Misdiagnoses are common especially in certain complex histologic varieties.

Imaging hallmarks are usually of multilobulated cysts with only one large cyst noted in few cases. The cysts are the glioneuronal elements and are located in the cortex or in cortical-subcortical white matter, with sometimes single satellite cysts located in the vicinity of these tumor, which are clearly separated. The cysts are either organised in a ball-like fashion or perpendicular to cortical surface, and are characteristically hypointense on T1 images and strongly hyperintense on T2 images. On FLAIR studies, they are noted to have a mixed signal intensity with majority of the lobuli within cyst being hypointense. The glioneuronal elements of the tumor may show contrast enhancement, which may vary on follow-up[13]. Calcifications are noted in approximately 10–30% of DNETs, mostly in the deeper parts of tumor, in the vicinity of contrast enhancements and in the vicinity of hemorrhagic areas[13].

Histopathology and molecular studies reveal a tumor with glioneuronal elements with cells resembling oligodendrocytes adherent to axon bundles and neurons floating in myxoid interstitial fluid. If purely the glioneuronal elements are present, they are referred to as simple DNET variant. Complex DNET variants may contain additional glial nodules that resemble astrocytomas or oligodendrogliomas with foci of cortical dysplasia, calcifications and hemorrhages. A third type, the so-called nonspecific or diffuse type are not generally accepted as DNET variant[13,14]. DNETs belong to the WHO grade I tumors with rare recurrences. Recurrences in DNETs may be more pronounced in the complex variety in which the following characterizations of early onset seizure and extratemporal locations are noted. Malignant transformations in a previously benign DNET has been described[15].

BRAF alterations and RAS/ERK, PI3K/AKT, and mTOR signaling pathway activations are noted in 30–50% of DNETs[14].

Temporo-mesial LEAT have a widespread epileptic network with complex mechanisms of epileptogenesis. From an epilepsy surgery-oriented strategy, LEAT may have excellent seizure outcome and therefore surgical treatment should be offered as early as possible, irrespective of their pharmaco-resistant properties, Hence avoiding the repercussions of uncontrolled seizures as well as the unwanted side effects of prolonged medical therapy thereby also factoring in the rare risk of malignant transformation of these tumors.

Epileptic seizure incidence varies depending on the tumour location and histology. Furthermore, low-grade tumors are often found to be more epileptogenic than high

grade tumors[16-21]. The spectrum of LEAT is currently expanding not only for the recognition of new and rare histologies, but also to inculcate tumors with mixed histological features[22-26].

LEAT are found mainly to arise in the temporo-mesial structures in the region of allo-isocortical transition, encompassing more frequently a neuronal differentiation which maybe because of their proximity to the hippocampal granular layer where neurogenesis during adult life occurs[27-33]. They are often large tumors, with a propensity to develop seizures when located around the temporal or frontal lobes[17,34]. These glioneuronal tumors are composed of particular cellular components with hyperexcitable neurons which are functionally connected to the excitatory circuits, and neurochemical profiles that may play a vital role in epileptogenesis[35]. Stereo EEG recordings from within these tumors have decoded the intrinsic epileptogenic capacity of these tumors[36,37]. Furthermore, the immunohistological studies show increased expression of glutamate receptor subtypes which could lead on to hyperexcitation in the neuronal regions of these tumors[38,39]. Another mechanism for sustainence of epileptogenesis is noted to be the inequilibrium across excitatory and inhibitory receptors namely the exagerrated expression of mGluR5 and downplaying of several GABA-A receptor (GABA- AR) subunits leading to an impairment in GABAergic inhibition[40,41]. Also, ionic homeostasis disturbances could add to increased excitability in these glioneuronal tumors[42,43]. Other mechanisms of epileptogenesis could be due to the possible participation of inflammation secondary to tumorigenesis[44] which could decrease

the seizure threshold and initiate an epileptiform response[44-46]. Different mechanisms are known to cause an increase in neuronal excitability, that is by enhancing extracellular glutamate levels and also by functional modification of glutamate and GABA receptors. Furthermore in glioneuronal tumors, particularly gangliogliomas, inflammation is shown to alter blood-brain barrier (BBB), albumin egress and uptake in tumorigenic astrocytes[45,46]. Some studies have also shown an upregulation of mTOR pathway which is found to play a key role in cellular milieu responsible for epileptogenesis[47,48].

Other hypothesized mechanisms that upregulate excitability in gangliogliomas are hypoxia and acidosis, ionic changes, and hemosiderin deposition in the peritumoral region[17]. Enzymatic alterations in peritumoral regions may also impair synthesis and storage of neurotransmitters, finally contributing to tumor-associated epilepsy. The association of glioneuronal tumors with focal cortical dysplasia should also be considered in the epileptogenetic pathway of glioneuronal tumors which are elaborated in the subsequent session.

FOCAL CORTICAL DYSPLASIA AND LEATs

LEATs and associated focal cortical dysplasias are frequently co-existent in drug-resistant focal epilepsies and this association between LEATs and FCD could lead to a diagnostic dilemma. LEAT are commonly associated with Type IIIb cortical dysplasia according to the ILAE classification which, compared to focal cortical dysplasia Type IIb, are more difficult to identify on imaging[16,49,50,51] due to a larger anatomical lesion compared to what that is found on imaging[52,53]. Considering this

particular reason, the target of surgical resection should contain the epileptogenic zone defined based on radiological, clinical, neurophysiological and psychological parameters.

MOLECULAR BASIS OF LEAT

Molecular markers that may facilitate diagnosis of LEAT has been mentioned in the previous session. They may allow for differentiation of these tumors based on the following characteristics such as

(1) IDH1 and IDH2 mutations: which are common in low grade diffuse gliomas (70%-80%), while not present in glioneuronal tumors[54].

(2) LOH 1p/19q: which constitutes the diagnosis of oligodendrogliomas (> 70% of tumors), although they have not been detected in DNET, it serves a prominent role in cases where differentiation based on histological aspects does not permit a conclusive diagnosis[55].

(3) BRAF V600E mutations: frequently found in GG while the diffuse grade II gliomas harbour these very rarely[56]. The BRAF-mutant grade II diffuse gliomas also may present with refractory seizures frequently with temporal location and there is growing evidence of the role of this mutation linked to epileptogenesis[57]. Few studies have found that the BRAF mutations could be present in the cortical dysplasia associated with LEAT, suggesting its role in cyto-architectural dysplasia and tumorigenesis of LEAT[58].

INTRA-OPERATIVE ELECTROCORTICOGRAPHY (ECOG)

Wilder Graves Penfield and Herbert Henri Jasper, neurosurgeon and epileptologist respectively pioneered in the works on Electrocorticography at the Montreal Neurological Institute in 1950s[59]. The two had been in the works of developing the now called Montreal procedure, a surgical protocol used for severe epilepsy during which they developed electrocorticography.

Intraoperative ECoG has been used (1) to localise the irritative zone, (2) for cortical mapping of functions, and (3) to predict the success of epilepsy surgery.

ECoG helps to phenotype the site and extent of epileptogenic discharges. The potentials identified by ECoG helps localise epileptogenic zones, which could then be surgically removed, thereby preventing the origin of seizures. ECoG recording is similar to the scalp electroencephalogram recording with the advantage of negation of dispersions and attenuation of potentials by the cranium and scalp. Therefore, ECoG should allow for better localisation than scalp EEGs[60].

These are usually done as short recordings intra-operatively and therefore the possibility of ECoG detecting an ictal event is unlikely. Hence, ECoG is used to detect interictal epileptiform discharges for the identification of the regions of interest. ECoG helps to map focal interictal spikes rather than epileptiform discharges and has been used for over 4 decades in the context of epilepsy surgery. After the surgical resection is completed, ECoG recording would help to identify whether aberrant areas with discharges have been removed or not[61].

The advantages of ECoGs are: (1) flexible placement of electrodes; (2) recordings prior to and after resection to detect epileptiform activity; (3) direct electrical stimulation in order to identify and spare areas of eloquence[62,63].

ECoG is not an alternative for presurgical evaluation as prior lateralisation and localisation of the epileptogenic focus is warranted[64]. Intra operative ECoG has been evaluated extensively at epilepsy centres worldwide but the levels of evidence available are not ideal[65-67]. Mathern, Salanova, Gonzalez and other leading stalwarts in epilepsy surgery have investigated this aspect of epilepsy surgery, but several unanswered questions remain.

The fallacies associated with ECoG are that they capture only interictal discharges and also they depend on pre surgical testing to guide the placement of electrodes intraoperatively. The usage of ECoG extends the surgical time and cortical exposure which could result in higher morbidity including risk of infections.

The concept of “long-term epilepsy associated tumor (LEAT)” was introduced by Luyken et al. (2003) referring to tumors commonly encountered in surgical series of patients who have been investigated and treated for drug-resistant seizures for two years or more[68]. DNETs and gangliogliomas are the most common of these tumors. The relationship between the epileptic zone (area of origin of the epileptic seizure) and the irritative zone (area of maximum interictal epileptiform discharge) is not clearly understood and is still a matter of research interest[2,3]. The degree to which the two zones overlap, especially on the ECoG recording is unclear.

A primary objective of epilepsy surgery is to remove the ‘epileptogenic zone’, which is the region whose removal prevents the patient’s seizures (Luders and Awad, 1992), and ECoG is intended to assist the achievement of this aim[69]. But criteria for identifying such epileptogenic zones have not been established; and is generally assumed that the epileptogenic zone includes the region displaying interictal discharges (‘irritative zone’ in Luder’s terminology) together with the epileptogenic lesion, and the site of electrographic seizure onset if identified. Specifically, removal of the entire ECoG-defined irritative zone and abolition of all spike discharges following resection are neither essential nor compulsory of good outcome.

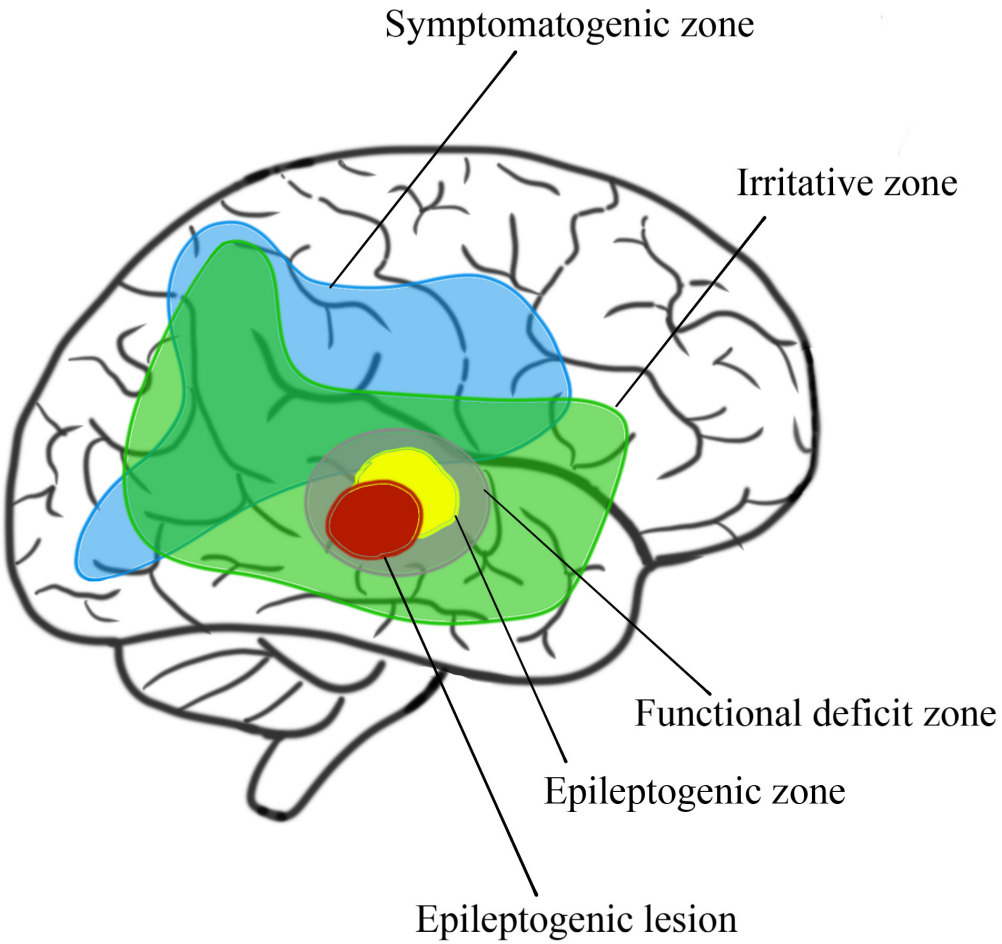

Figure 1. Schematic representation of the cortical zones in epilepsy.

It has been hypothesized that the frequency of this activity is proportional to the proximity to the ‘epileptogenic area’. Alarcon et al. found that the removal of this area lead to a good surgical outcome, even if areas of less frequent discharges were left untouched. If the area of maximal discharge was not completely resected, the surgical outcome was more likely to be poor.

Falconer et al performed surgical resection for temporal lobe epilepsy in 50 cases at the Guy's-Maudsley Neurosurgical Unit with monitoring of electrical discharges from the electrocorticography. He carried out resections over the main discharging areas alone based on ECoG and derived good outcome with 37 out of 50 patients having improvement in seizure more than 50% and 24 out of 50 being seizure free in the subsequent 2-7 years of follow up[70].

Jerome Engel, Jr. et al in 1975 following their study concluded that corticographic data are less useful, although some pathological correlations have been shown, and in one patient the necessary information was derived only from electrocorticography. Because surgical prognosis depends largely on the nature of the epileptic lesion, and because electrophysiological data appear to correlate better with pathological findings than with surgical results, it is suggested that these criteria be used in conjunction with other clinical criteria to arrive at a pathological diagnosis[71].

So N et al in their study conducted on 57 patients at the Montreal Neurological institute concluded that the consistent trend showing a significant correlation between the post-excision ECoG and the ultimate seizure control underlines the role of ECoG in determining the extent of surgical resection necessary for achieving the best possible results[72].

M E Fiol et al correlated the post-resection electrocorticograms (ECoGs) of 80 patients who underwent temporal lobectomy under general anesthesia for treatment of intractable complex partial seizures and found that Spontaneous "residual spikes" present after all resections, were present in 47% of patients who had no postoperative seizures or auras and occurred in 72% of patients with postoperative seizures (p less than 0.05). The location (convexity, mesial, or edge of resections) or the distribution (unifocal versus multifocal) of the residual spikes was not of prognostic value[73].

M C McBride et al studied the pre-resection and postresection intraoperative electrocorticograms of 76 consecutive patients undergoing resective surgery for intractable epilepsy to see if location, configuration, and discharge rate of epileptiform activity correlated with type and location of pathology of the resected specimens and outcome in regard to seizure control. The presence of spontaneous or activated spikes outside the resected area did not correlate with outcome from any surgery type. Persistence of 50% or more of the pre-resection epileptiform activity in the postresection electrocorticogram after temporal lobectomy correlated with poor outcome in 80% ($p \leq 0.03$), although the absolute amount of epileptiform

activity remaining in the postresection electrocorticogram did not correlate with outcome[74].

P Jennum et al in a combined study done at University of Copenhagen and University of Minnesota, on 64 patients evaluated with chronic subdural electrode array concluded that complete resection of the interictal and ictal field mapped with SEA's and absence of postresection spikes on operative electrocorticography are associated with an excellent seizure outcome[75].

A Tuunainen et al evaluated the role of different EEG methods with respect to postoperative clinical follow-up in 32 non-lesional epilepsy patients who had undergone temporal lobectomy and concluded that the postresection ECoG abnormalities were not associated with clinical outcome[76].

G D Cascino et al investigated the relationship between electrocorticography (ECoG), quantitative magnetic resonance imaging (MRI), and surgical outcome in 165 patients with intractable non-lesional temporal lobe epilepsy (NLTLE) where in the extent of the lateral temporal neocortex resection (LCR) was guided by ECoG and the side of surgery. They deducted that the topography of the acute intracranial spikes did not correlate with operative outcome ($p > 0.5$) and was independent of hippocampal volumetric studies ($p > 0.5$). The post-excision ECoG was also shown not to be of prognostic importance ($p > 0.5$)[77].

Stefan et al studied the results of intra-operative cortical EEG recordings (ECoG) in 30 patients with medically refractory complex partial seizures submitted to temporal

lobectomy and found that ECoG provides reliable intra-operative mapping of the epileptogenic brain tissue to be excised[78].

A Palmini et al described that cortical dysplastic lesions are highly and intrinsically epileptogenic, and that intraoperative ECoG identification of this intrinsically epileptogenic dysplastic cortical tissue is crucial to decide the extent of excision for best seizure control in their study in which three-fourths of the patients in whom it was entirely excised had favourable surgical outcome[79].

M L Tsai et al in their study (Part I) on 72 patients with medically intractable epilepsy found that pre-resection ECoGs provide information on the epileptogenic dysfunction that involves most of the temporal lobe of patients with medically intractable TLS. Later in Part II study, they quantified retrospectively the interictal epileptiform discharges (IEDs) detected visually in the electrocorticograms (ECoGs) of 42 patients undergoing successive stages of anterior temporal lobectomy for medically intractable temporal lobe seizures (TLS) and came to the conclusion that the post-resection foci were significantly less numerous and extensive, and attained smaller maximal voltages, than did foci before and after first resection[80].

Study performed by O Kanazawa et al Among 87 consecutive patients operated on under local anaesthesia revealed that the pre-resection spike quantity fails to distinguish outcome groups and that the absolute quantity of post-resection spikes and change from pre-resection quantity in any region did not correlate with outcome except for the insula, where relatively abundant spikes portended favourable

outcomes. Post-resection electrographic seizures were rare but occurred equally in all outcome groups[81].

T H Schwartz et al performed both pre- and postresection intraoperative ECoG on 29 consecutive patients with medial temporal lobe epilepsy who underwent standard nontailored resections by one surgeon and found that eleven patients (38%) had residual spike discharges after resection, and 18 patients (62%) had new spikes revealed by the postresection ECoG. Neither of these findings nor the mean spike frequency of residual or new spikes related to seizure outcome. Persistent spikes increased in frequency after resection in all outcome groups. They concluded that ECoG monitoring of interictal epileptiform activity intraoperatively is not useful in the surgical treatment of patients undergoing standard resection for medial temporal lobe epilepsy with magnetic resonance imaging evidence of mesial temporal sclerosis[82].

C H Ferrier et al reviewed 35 patients who underwent frontal lobe resections for the presence of epileptiform discharges in intraoperative electrocorticograms (ECoGs) and the nature and extent of neuropathologic abnormalities and found that the seizure patterns were significantly more common in patients with cortical dysplasia, and their abolition on postresection ECoG recordings was associated with a favourable surgical outcome. They also concluded that the persistence of sporadic ECoG spikes and incomplete removal of histologic abnormalities did not affect outcome significantly[83].

G M McKhann 2nd et al in their study observed that intraoperative hippocampal ECoG can predict how much hippocampus should be removed to maximise seizure-free outcome, allowing for sparing of possibly functionally important hippocampus in 140 consecutive patients who underwent surgery for mesial TLE with pathological diagnoses of either mesial temporal sclerosis with neuronal loss (MTS group) or mild gliosis without neuronal loss[84].

Anesthesia considerations during Epilepsy surgery

All agents used in general anaesthesia have effects on intraoperative ECoG signals. propofol (2,6 di-isopropyl phenol) is a commonly used intravenous form of anaesthetic agent, especially in awake surgeries, due to its short half-life[85]. A recent report (Zijlmans *et al*., 2012) showed that reduction of the dose of propofol led to increased number of pathological high-frequency oscillations (pHFOs) captured during intraoperative ECoG recording[86].

Deep anaesthesia may mask the generation of spontaneous abnormal spikes or pHFOs that the intraoperative monitoring is aimed at capturing. As a result, intraoperative ECoG is ideally performed on awake patients under local anaesthesia. However, this regimen may not work for paediatric patients, non-cooperative adults, or patients at risk of hypoventilation (*e.g*. obese body habitus or obstructive sleep apnoea), and may not be completely necessary if the anaesthetic can be lowered sufficiently. Using light anaesthesia and holding short- acting anaesthetic agents about 10-20 minutes prior to recording can be implemented[86].

TUMORAL EPILEPSY

In patients with tumoral epilepsy, the epileptogenic zone is distinct from the tumor[87]. Both the lesion and the perilesional tissue need to be completely excised 88,89 for optimal seizure freedom.

Intraoperative hippocampal EcoG can predict the extent of hippocampal resection required to achieve maximum seizure freedom[90]. Thus, functionally normal hippocampus can be preserved and postoperative memory decline minimised with tailored temporal resections[91] using the data from hippocampal EcoG recordings.

In patients with cavernomas, EcoG guided resection offers the best seizure control[92], as it helps in identification and complete excision of the highly epileptogenic hemosiderin rim[93].

Jooma et al.[94], Sugano et al.[95] have found seizure freedom of 93% and 90.9%, respectively.

Englot et al.[96] in their quantitative and comprehensive literature review found that 80% of tumoral epilepsy patients are completely seizure free post-surgery. Ravat et al found that the seizure freedom in tumoral epilepsy without ECoG is 80%, while the same is 89.5% with ECoG in their study[97].

Berger et al retrospectively analysed forty-five patients with low-grade gliomas and intractable epilepsy with respect to preoperative seizure frequency and duration, number of antiepileptic drugs, intraoperative ECoG data (single versus multiple foci), histology of resected seizure foci, and postoperative control of seizures with

or without antiepileptic drugs and concluded that ECoG is advocated, especially in children and in any patient with a long-standing seizure disorder, to maximise seizure control while minimising or abolishing the need for postoperative antiepileptic drugs[98].

R Wennberg et al compared the results of ECOG performed in 22 patients with intractable frontal lobe epilepsy and a circumscribed frontal lobe structural lesion with postoperative seizure control and identified that the post-operative seizure control in lesion-related FLE is assured in the setting of complete lesion resection with pre-excision EA recorded from < or 2 gyri and no post-excision EA distant to the resection border; complete lesion excision is of paramount importance[99].

Hidenori Sugano et al conducted study on thirty-five medically intractable epilepsy patients with temporal-lobe benign mass lesions, who had been surgically treated including their relationship between resection of the epilepsy focus using intraoperative electrocorticography and seizure outcome and observed that the even after the complete removal of temporal-lobe-mass lesions, a high frequency of residual spikes was obtained from the hippocampus. Effective surgical seizure control was achieved by carrying out additional procedures on the affected hippocampus. To detect seizure foci surrounding the lesion, especially over the hippocampus, intraoperative electrocorticogram monitoring was shown to be an effective technique[100].

Hideki Ogiwara et al retrospectively analyzed seizure outcome and surgical results of 30 pediatric patients with ganglioglioma treated with resection and concluded

that lesionectomy with adjacent temporal neocortex resection using intraoperative ECoG provided good seizure control of pediatric temporal ganglioglioma. For extratemporal ganglioglioma, lesionectomy alone can provide fairly good seizure control. Considering the memory function of the hippocampus, lesionectomy with adjacent temporal neocortical resection can be a safe, feasible, and effective treatment option for epileptogenic gangliogliomas in pediatric patients[101].

Marco Giulioni et al retrospectively reviewed 15 children surgically treated for glioneuronal tumors associated with epilepsy and observed that lesionectomy may provide good long-term seizure control in the majority of children with epileptogenic glioneuronal tumors[102].

In a retrospective study conducted by Wen-han Hu et al, 55 patients with epileptogenic gangliogliomas underwent surgery. They concluded that the surgical treatment is effective and safe for patients with epileptogenic gangliogliomas. Early surgical intervention is necessary for achieving early seizure control. Neither intraoperative ECoG nor IOUS necessarily leads to better seizure control, although the latter can be helpful in achieving complete tumor resection. Simple lesionectomy is sufficient for favorable postoperative seizure outcome[103].

A Consales et al collected clinical data through a database of 22 patients between the age range at surgery of 10 months-16 years with glioneuronal tumor associated epilepsy and concluded that the primary aim of the surgery for epileptogenic glioneuronal tumors should be to remove the lesion and to obtain a complete seizure

control. However, if a complete tumor resection cannot be carried out, a subtotal removal of the lesion can equally provide satisfactory results[104].

An earlier study (Tran et al., 1995) had found no such correlation. Therefore, the quality of evidence in this matter needs evaluation by a prospective randomised study[105].

Few studies in India have been attempted to evaluate the ECoG utility in lesional epilepsy notably the study by Tripathi et al from AIIMS, Delhi[60]. Another by Radhakrishnan A. et al (from our group) had investigated the prognostic factors for seizure outcome benefits in LEATS[61]. However, a prospective randomised study evaluating this research question has not been done before in India.

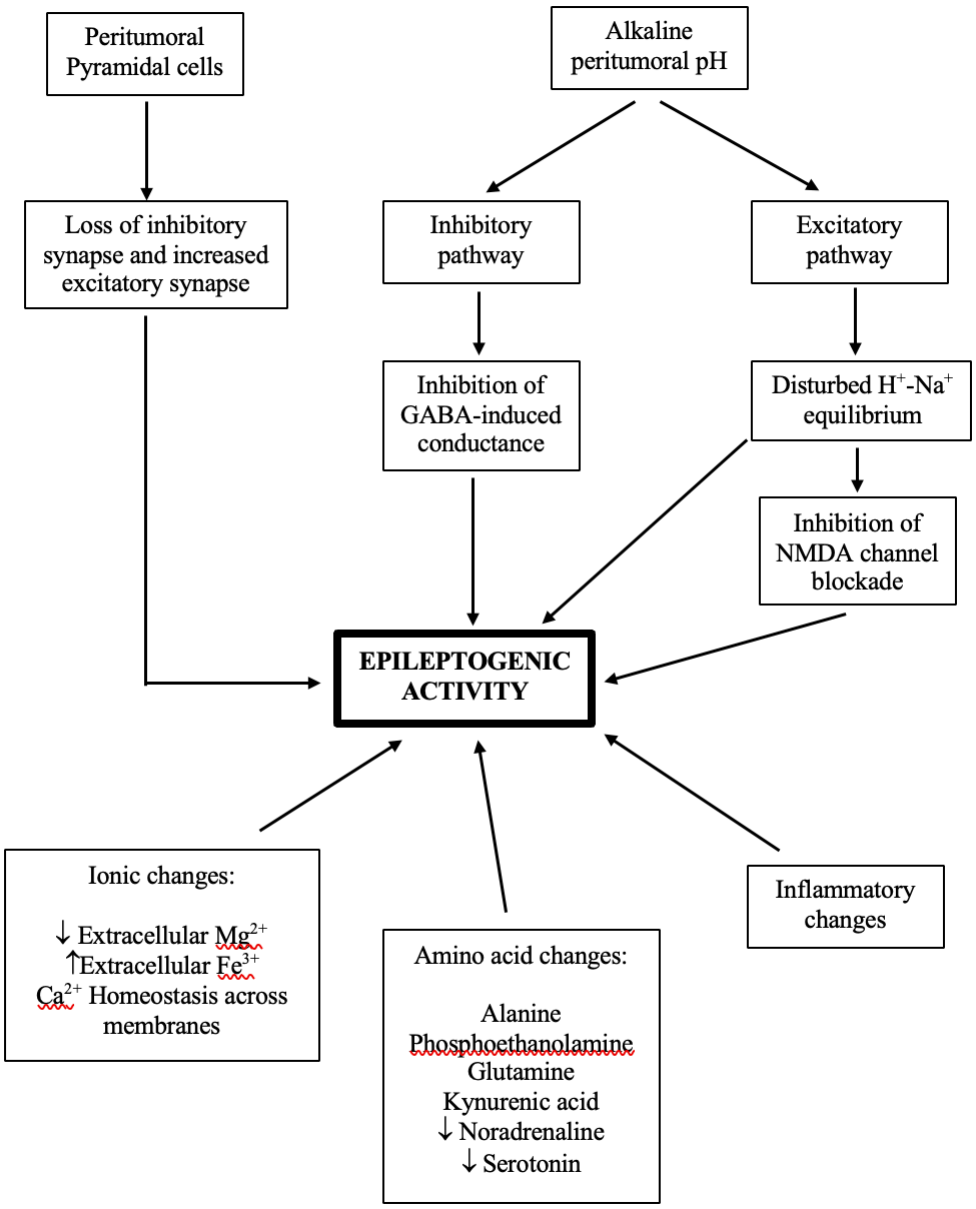

Figure 2. Pathophysiology of tumor epilepsy.

The identification of lesions associated with and responsible for epilepsy are identified using pre-surgical evaluation protocols set forward based on standardisations over the last few decades of research and development. Needless to

say that these practise protocols overlap with various centres. The common pre-surgical evaluation methods and their associated advantages and disadvantages are mentioned in the following table.

Investigation	Relevance
Pre-operative	
Electrophysiological studies	
EEG	Ictal discharge frequency correlates with degree of
VEEG	Temporal onset of seizures and interictal activity over
Imaging	
CT	Tumor localisation
MRI	Tumor localisation and detection of subtle lesions
PET	Changes in metabolism and chemistry
fMRI	Localisation of eloquence
Others	
Neuropsychology	Localisation and assessment of severity of lesions
Wada test	Preservation of language and memory by identifying
Intra-operative	
ECoG	Interictal discharge identification
SEEG	Identification of electrical activity in between and during
Ultrasonography	Tumor localisation and identification of anatomical landmarks
Cortical mapping	Precise localisation of eloquence

Table 1. Pre-surgical tests and their significance.

Seizure outcomes for low-grade epilepsy- associated neuroepithelial tumors

Multiple studies have analysed the seizure outcome in patients undergoing epilepsy

surgery for low grade tumors. A literature search for such studies revealed the following data.

Study details	Year of study	No. of patients	Seizure free outcome	Poor outcome associated factors
Yang et al.	2019	39	66.7%	Presence of satellite lesions on an MRI scan
Ko et al	2019	58	87.9%	Subtotal resection
Faramand et	2018	92	80.4%	Subtotal resection
Daszewicz et al	2018	52	86.5%	Age of 56 yr at surgery Duration of epilepsy>1 yr
Ehrstedt et al	2017	25	64%	Subtotal resection
Brahimaj et al	2014	18	44.4%	Greater number of AEDs tried before surgery
Ramantani et	2014	29	75.9%	Subtotal resection
Babini et al	2013	30	86.7%	Younger age at seizure onset Tailored surgery (i.e, extended resection for epileptogenic foci) for temporal lobe tumors
Garcia-Fernandez et	2011	21	85.7%	Subtotal resection
Utiel-Sibony et al	2011	41	82.9%	Presence of generalized EDs in an EEG
Ogiwara et al	2010	30	90%	None
Minkin et al	2008	24	83.3%	Presence of generalized seizure
Nolan et al	2004	26	84.6%	Subtotal resection

Table 2. Previous studies of epilepsy surgery in low grade tumors with outcome.

MATERIALS AND METHODS

Study design, patient selection and randomization

A single-center, prospective randomised controlled trial registered under the Clinical Trial Registry of India (CTRI/2022/03/041067) after approval by the Institute Review board (IRB). The study included all consecutive patients with LEATs (in non-eloquent locations) and drug resistant epilepsy who underwent primary surgical resections at our tertiary comprehensive epilepsy care center between June 2020 and January 2022. The study group were randomised (using a computer-generated lot system) into 2 groups namely Group E (ECoG) underwent gross total resection (GTR) with ECoG assistance and Group NE (no ECoG) underwent gross total resection(GTR) without ECoG assistance. Group E patients further underwent tailored resections, if necessary, as per ECoG practice protocols (*Figures 1,2).* Re-operations for failed seizure control or tumor recurrence and eloquent cortex lesions were excluded from the study.

Pre-surgical work up

All the patients underwent a standard presurgical work up for medically refractory epilepsy as per institutional protocols and established standards of care. The detailed presurgical work up for LEATs at our centre has been described in an earlier publication[106].

Peri-operatively, patients were continued on the same antiepileptic drugs (AED's) and was tapered during follow up visits based on the post-operative seizure burden.

The surgical outcome was interpreted for seizure outcome using Engel grading system and adverse event profile evaluated at 3,6,12 months follow up[107].

Surgical candidacy selection

The ILAE definition of drug resistant epilepsy was used for initiating a pre-surgical work up. In case of refractory status epilepticus or significant seizure related disability, pre surgical evaluation was initiated earlier .Our protocol included a detailed clinical history with seizure semiology and examination, long-term video-EEG monitoring, 1.5 T magnetic resonance imaging (MRI) and neuropsychological evaluation. In addition to our routine MRI protocol, we undertook additional three-dimensional fluid attenuation inversion recovery (3D-FLAIR) and susceptibility weighted imaging (SWI) MRI sequences, and functional MRI (fMRI) for motor and language functions in patients with lesions having motor or language area proximity. Patients were selected for resective surgery based upon the concordance of clinical-EEG-imaging findings after an elaborate discussion in the multidisciplinary patient management conference

Anesthesia protocol for ECoG

Awake surgery was not performed in the study patients as eloquent cortex lesions were excluded. Anti-aspiration prophylaxis was usually administered with Ondansetron and Pantoprazole as per institutional protocol and sedative premedication with benzodiazepines were avoided. Anesthesia was generally induced with sevoflurane or propofol 1.5-2 mg/kg depending on the presence of intravenous access, along with 2 μg/ kg of Fentanyl and 0.1 mg /kg of Vecuronium.

Maintenance of anesthesia was with sevoflurane 0.7-0.8 MAC (Minimum alveolar concentration) in Air, oxygen mixture and infusion of Fentanyl 1-2 µg/ kg/hr and atracurium 0.3 mg/kg/hr. Sevoflurane was reduced to < 0.5 MAC at the time of ECoG monitoring, which was even switched off if the ECoG traces were not optimal and supplemented by additional boluses of fentanyl. Bolus doses of propofol were avoided. During reversal, the anesthetics were stopped and muscle relaxation reversed with neostigmine (0.5 mg/kg) and glycopyrrolate (0.1 mg/kg).

ECoG technique

The ECoG recordings were performed using a 32-channel machine (Nicolet, Viasys, USA). Recording from neocortical surfaces representing the area of interest were recorded pre-resection using a 20-contact grid electrode and post-operative recordings were obtained from the margins of resection using a standard 4-contact strip electrode for five minutes duration. The reference electrodes were placed away from the surgical field on the scalp. An EEG pattern suggestive of ictal onset was marked by a background of alpha waves mixed with slower activity or alpha waves with faster rhythms. Post primary resection electrical activity was classified as 'clean' (no spikes), intermittent non rhythmic spikes and continuous rhythmic spikes. Persistent frequent spikes on post-resection ECoG was tackled with tailored resections after factoring in risk versus benefit of “chasing the spikes” and consideration of the proximity to eloquent cortex. Interpretation of the ECoG recordings were done by one of specialist epileptologists (Dr Ramsekhar Menon, Dr Ashalatha Radhakrishnan, Dr Ajith Cherian).

Surgical Strategy

The surgical resection techniques were standardised and performed by the same team (Dr Mathew Abraham, Dr George C Vilanilam). Based on the clinico-electrical-radiological localisation of the 'epileptogenic zone', the surgical strategy involved any one of the following,

1. *Lesionectomy*- Resection involving a focal radiological/ morphological abnormality/ lesion

Example: Ganglioglioma resection

2. *Extended lesionectomy*-Resection involving a focal radiological/ morphological abnormality/ lesion with surrounding lesions (focal cortical dysplasia (FCD), gliosis) having epileptogenic potential (morphological/ radiology based).

Example: Resection of a ganglioglioma with surrounding FCD (ILAE type III B)

3. *Intra operative ECoG based additional tailored resections*-

Post resection ECoG with continuous rhythmic spikes, prompted additional resections at the borders without extension into eloquent areas. The end point for tailored resections was the eloquent cortex limits or a 'clean ECoG'(no persistent rhythmic spikes).

Pathological examination

Four-micrometer-thick histologic sections were generated from 10% formalin fixed, paraffin-embedded tissue and stained with hematoxylin and eosin (H&E) by a specialised neuropathologist (DN). Special stains such as Cresyl violet, Bodian and Luxol fast blue-hematoxylin eosin and immunohistochemical stains such as Neurofilament protein (NFP), synaptophysin, epithelial membrane antigen(EMA), glial fibrillary acid protein (GFAP), NeuN, chromogranin (Novacastra, Newcastle upon Tyne, UK; 1:100 dilution) etc were used as and when indicated. WHO classification of CNS tumours (Louis et al., 2016) and the ILAE classification of cortical dysplasia (Blümcke et al., 2011) was followed.

Post-operative assessment

Regular clinical follow up was done at 3 ,6 and 12 months after surgery and at yearly intervals thereafter. Seizure outcome (Engel score), late sequelae/ adverse events and quality of life parameters were assessed. Post operative CT scan was done within a day of the surgery to look for any surgical operative site complications and for a gross assessment of the adequacy of resection. Post-operative MRI to assess completeness of resection and scalp EEG were done at 3-6 month post-surgery. These were evaluated to assess completeness of lesion resection and background epileptiform activity. Decisions to taper anticonvulsants were highly individualised and based on seizure outcome, additional unresected epileptogenic lesions, adequacy of resection and background EEG epileptiform activity.

Class I	**Free of disabling seizures.**
IA	Completely seizure free since surgery
IB	Non disabling SPS only since surgery
IC	Some disabling seizure after surgery; free of disabling seizures for at least 2 years
ID	Generalized convulsions with AED withdrawal only.
Class II	Rare disabling seizures
IIA	Initially free of seizures, but has rare seizures now
IIB	Rare disabling seizures since surgery
IIC	More than rare disabling seizures after surgery, but rare seizures for at least 2 years
IID	Nocturnal seizures only.
Class III	Worthwhile improvement
Class IV	No worthwhile improvement.

Table 3. Engel's seizure outcome scale.

STATISTICAL ANALYSIS

For nominal and ordinal independent variables, we performed the cross-tabulation, chi-squared tests, and Fisher's exact tests (when the cells had an expected number less than 5) to analyse categorical variables. In the case of quantitative variables, we performed the t-test and ANOVA tests. If more than two groups were tested, we performed interclass post hoc tests, including Bonferroni's correction. For calculation of effect sizes, the odds ratio (OR) was used for categorical data. All tests were two-tailed and was analysed using SPSS Software version 24.0 (IBM SPSS Statistics).

RESULTS

Between June 2020 and Jan 2022, a total of 42 patients underwent primary surgery for LEATs in our institute. Prior to surgery, patients were randomised into Group E (ECoG group) or Group NE (Non ECoG) group(Fig 1). Group E (ECoG) had 23 patients. Group NE (No ECoG) had 19 patients(Fig 2) .In the ECoG arm, 6 out of 23 (26.08%) patients further underwent tailored ECoG based additional resections. (Table 4,5,6)

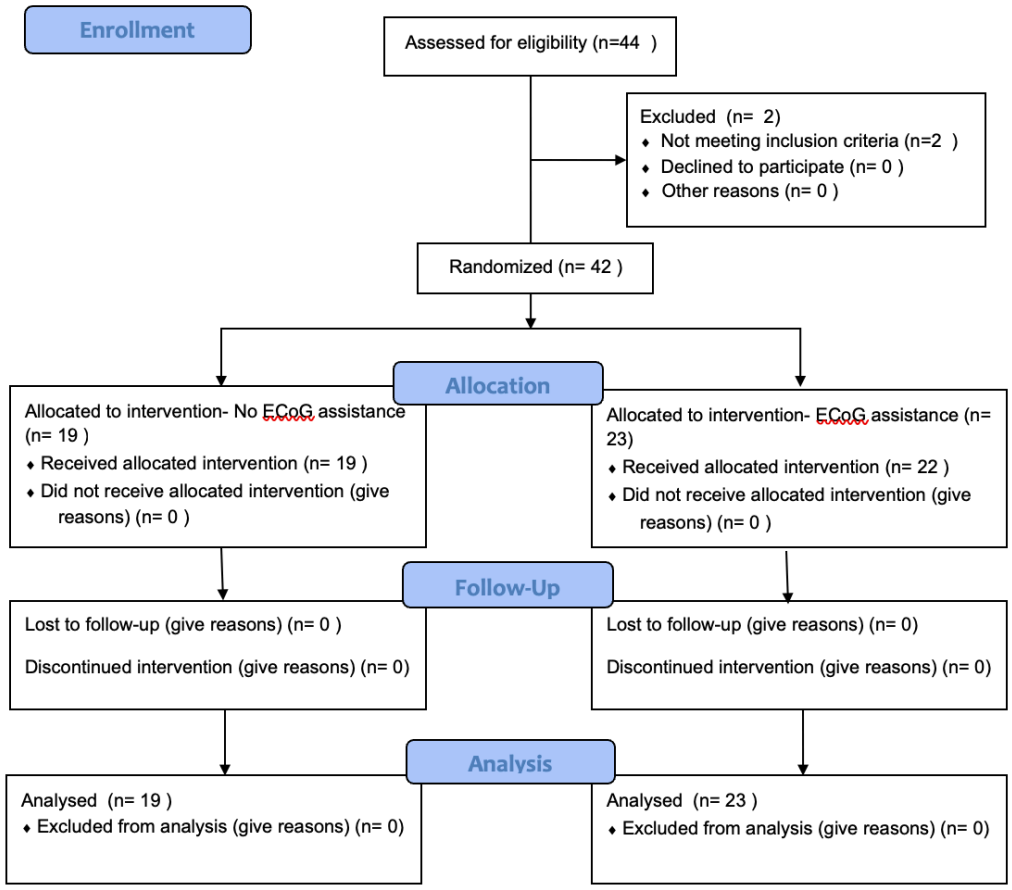

Fig 3. CONSORT flow diagram: Randomisation schema

Clinical characteristics:

The mean age of the study group was 22 years (SD 12) which included 27 males (64.28%) and 15 females (35.71%). The study group consisted of 17 pediatric (40.47%) and 25 adult patients (59.52%).

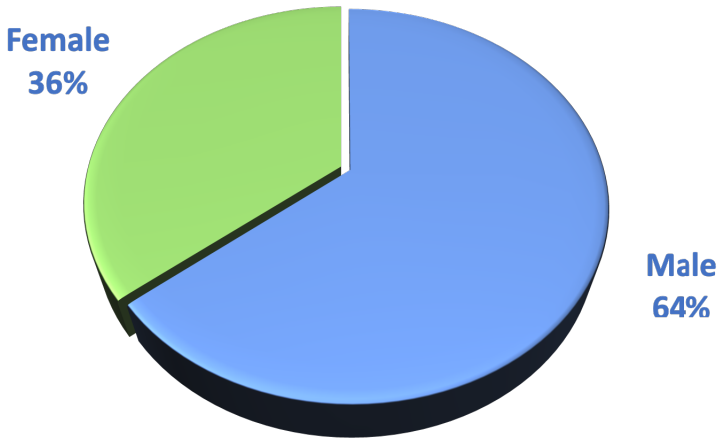

Figure 4. Gender distribution of study patients.

The ECoG cohort had 12 (70.58%) males and 5 females (Table 1). The mean duration of epilepsy was 8.2 years (SD 7.9 years) in the non-ECoG group and 7.9 years in the ECoG group (SD 7.3 years). While the non-ECoG cohort had more left sided lesions(11/19), the ECoG group had 12 out of 23 left sided lesions.The temporal lobe was the most common site of the lesion in both groups (NE and E)

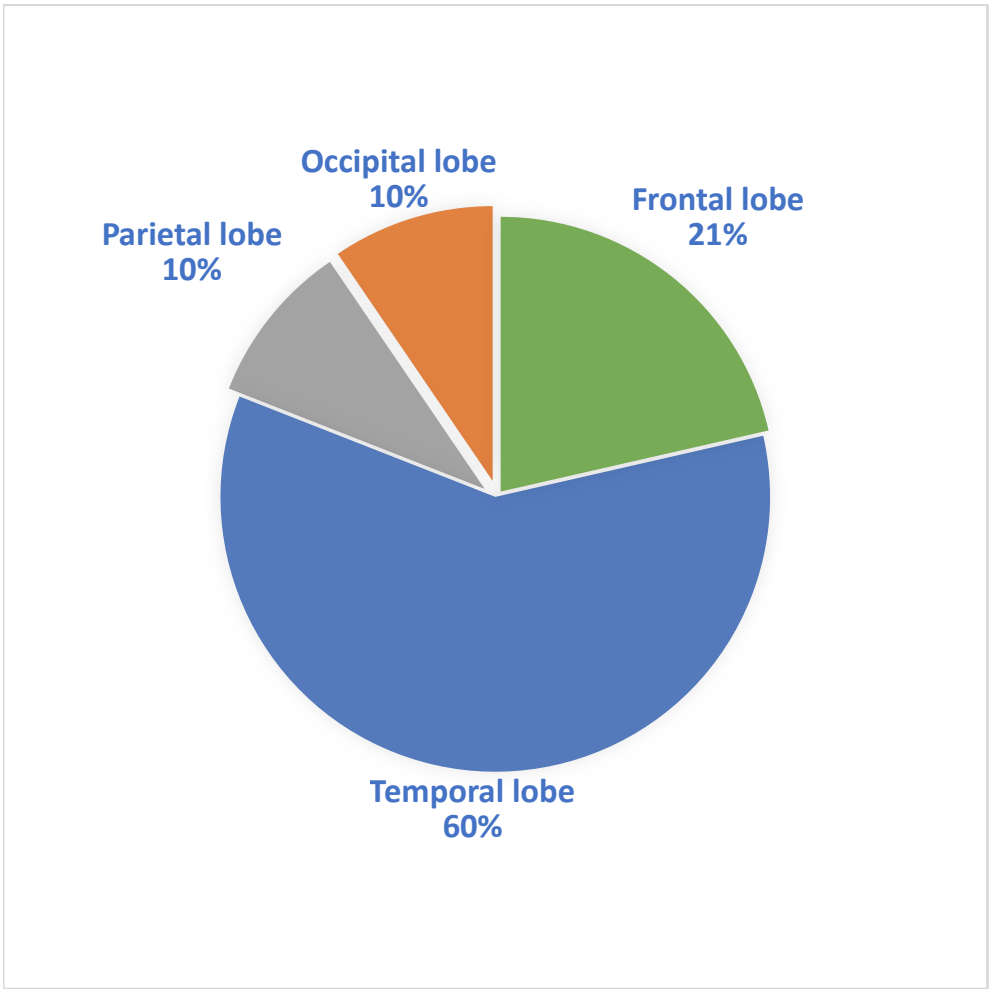

Figure 5. Topographical distribution of the lesions.

Mean total number of anti-epileptic medications pre-operatively used were 2.059 ± 1.144 and the average post operative duration of hospital stay was 4.4 days in the whole cohort. No patients underwent chronic long term invasive EEG monitoring.

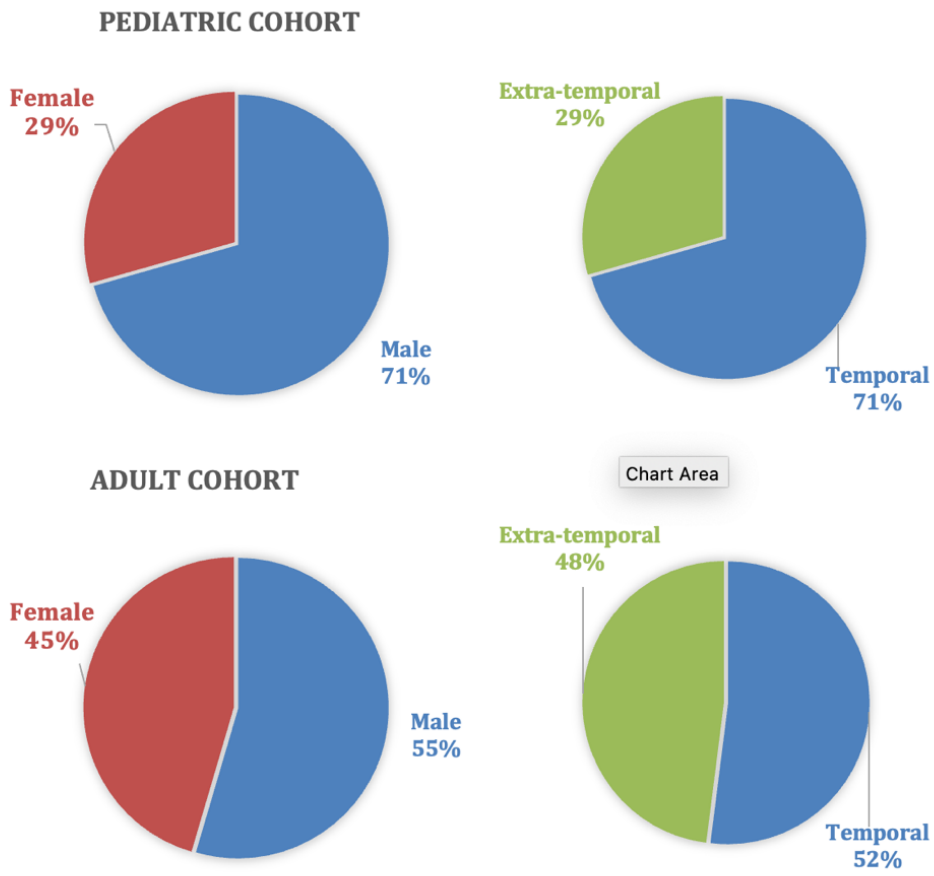

Figure 6. Distribution of gender and lesional location between pediatric and adult cohorts.

Age Category	Pediatric	Adult	Total	p-value
Location				
Temporal	12	13	25	0.228
Extra-temporal	5	12	17	
Total	17	25	42	

Table 4. Distribution of lesions into temporal and extra-temporal locations between pediatric and adult cohort.

Surgical Resection and Histopathology

All the 42 patients in the study group underwent gross total resections(GTR), with ECoG assistance used in 23 patients(14 children, 9 adults) as per randomisation. Further on, 6 patients from the ECoG arm respectively, underwent ECoG guided tailored resections.

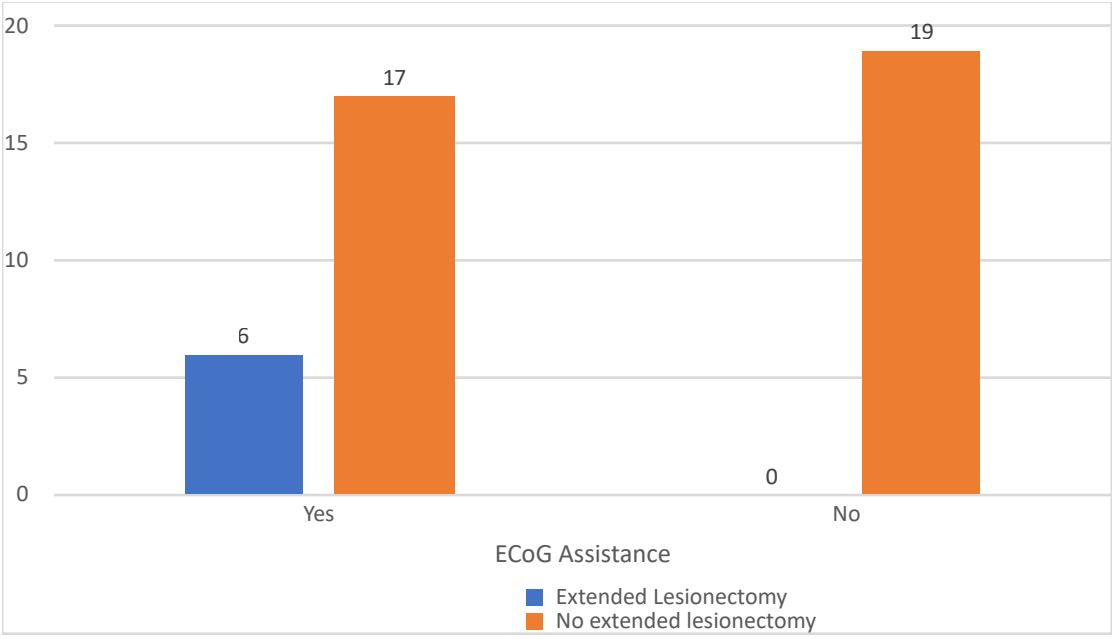

Figure 7. Distribution of patients between ECoG assistance and conduction or non-conduction of extended lesionectomy

Extended Lesionectomy	Yes	No	Total	p-value
ECoG Assistance				
Yes	6	17	23	0.016
No	0	19	19	
Total	17	25	42	

Table 5. Distribution of patients between ECoG assistance and conduction or non-conduction of extended lesionectomy in the total cohort.

59.5% of the patients had temporal lesions in the whole cohort. Ganglioglioma was the commonest histology (11/17 children and 20/25 adults) followed by DNET. 73.68% of non-ECoG patients (n=14) had Ganglioglioma compared to 26.31% cases of DNET (n=5) and 72.72% of ECoG patients (n=16) had Ganglioglioma compared to 22.72% cases of DNET (n=5) and one case of PLNTY (Polymorphous low-grade neuroepithelial tumor of the young). The seizure outcome difference between these pathologies were not found to be statistically significant (p= 0.786).The mean number of additional tailored extensions were 1.45 per tailored resection patient. The additional tailored resection specimen was unremarkable histologically in 3 patients. The surgical resection was completed based on morphological and anatomical limits in the non-ECoG group (n=19). In the ECoG arm, the resection limit was reached based on eloquent cortex proximity in 4 patients, no rhythmic ECoG spikes in 13 patient and 6 underwent further tailored extensions.

Seizure outcome and adverse event profile

85.71% of cases (n=36/42) had an Engel Ia outcome following resection compared to 11.90% of cases (n=5/42) with Engel Ib outcome and one patient with Engel II seizure outcome in the whole cohort.

	Non- ECoG Group (NE)	ECoG Group (E)
Number (n)	19	23
Age (in years)	20.84	23.13
Mean seizure duration (years)	4.47 ± 4.53	10.82 ± 8.37
Seizure outcome		
Engel Class I	18	23
Engel Class II	1	0
Engel Class III	0	0
Engel Class IV	0	0
Mean Tumor Volume (cm3)	20.26 ± 27.89	22.02 ± 53.69
Histology		
Ganglioglioma	14	17
DNET	5	5
PLNTY/Others	0	1
Tailored as per ECoG	0	6
Number of tailored extension of resections per patient (mean)	0	1.49
Histology of tailored resection specimen (n=6)		
• Tumor	0	2
• Tumor with cortical dysplasia	0	1
• Only Cortical dysplasia	0	0
• **Unremarkable**	0	3
Primary Surgical Resection completion limit		
• Anatomical/Radiologica limits reached	18	0
• Eloquent cortex limit reached	0	4
• 'Clean' ECoG(No rhythmic spikes)	0	13
• Additional tailoring	0	6

Adverse events		
Minor	5	4
Major	0	1
Mean follow up (months.)	15.70 ± 6.14	12.97 ± 5.90

Table 6. Baseline and outcome characteristics in Non-ECoG and ECoG group.

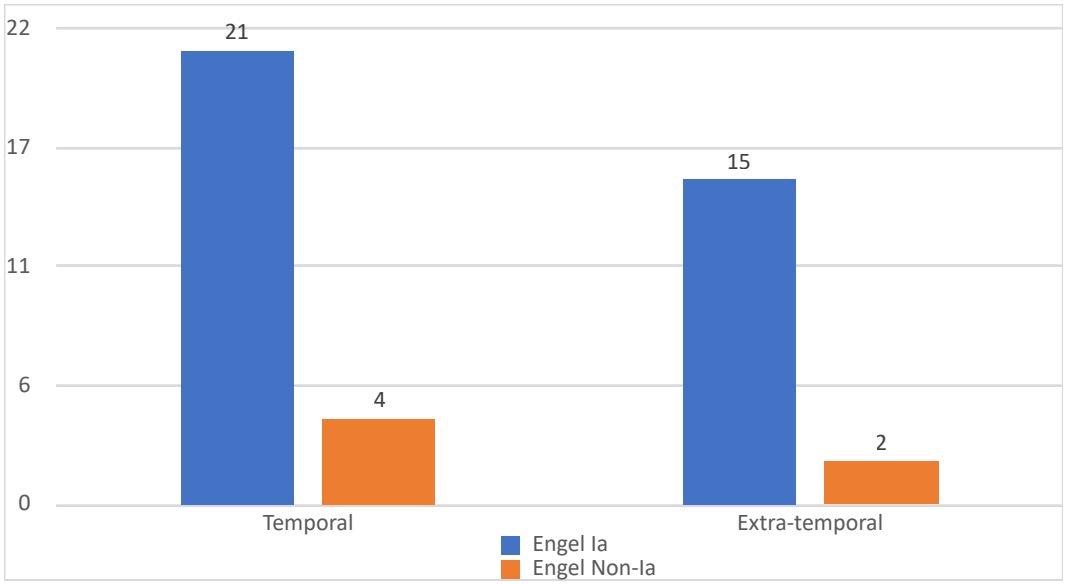

Figure 8. Seizure outcome scale comparison between temporal and extra-temporal lesions.

Engel score	Ia	Ib + II	Total	p-value
Location				
Temporal	21	4	25	0.700
Extra-temporal	15	2	17	
Total	36	6	42	

Table 7. Seizure outcome scale comparison between temporal and extra-temporal lesions.

Six adverse events were noted in ECoG group compared to five in non-ECoG group. Four out of 23 patients in the ECoG group, had a minor adverse events like operative cavity hematoma (< 15 cc) which did not warrant surgical intervention (n=2) and focal neurological deficits in the form of superior quadrantanopia (n=2). The patients with visual deficits belonged to the cohort that underwent additional tailored resection. One patient developed operative site extradural hematoma which was tackled by re-exploration and hematoma evacuation. In the non-ECoG cohort, 4 patients had minor adverse events.

Follow up and Seizure outcome

The mean follow-up period was 15.68 months in non-ECoG group (SD 5.95 months) and 13.21 months in ECoG group (SD 6.31). Among non-ECoG patients, 78.94% (15/19) had an Engel Ia outcome during the mean follow up period, followed by three cases with outcome of Engel Ib and one case with Engel II score. Among ECoG patients, 91.30% (21/23) had an Engel Ia outcome during the mean follow up period, followed by one case each with outcome of Engel Ib and Ic score. There is no statistically significant difference in seizure outcome benefit in both the ECoG and non-ECoG arms.

Peri-operative anti-epileptic medication usage

Mean number of anti-epileptic medications used in the pre-operative period at the time of surgery was 1.84 ± 0.89 in non-ECoG group compared to 2.13 ± 0.96 in ECoG group. Following surgery, at 3 months post-operative period, the average

number of antiepileptic medications used were 1.42 ± 0.96 in non-ECoG group compared to 2.00 ± 1.04 in ECoG group. In non-ECoG group, three patients had reduction in the number of antiepileptic medications at the end of 3 months follow up with 3 patients having complete discontinuation of medications during the follow up period in comparison to two each in ECoG group.

An illustrative case (16 year old boy) with a right temporal ganglioglioma and drug resistant epilepsy has been depicted in Annexure (Figure 8-12).

DISCUSSION

Among the pathological substrates in surgically remediable epilepsy, LEATs has the best outcome and these are even better in children. From an oncological perspective too, LEATs though WHO grade I and II tumors are treated surgically in view of their potential to transform to higher grade tumors[61,68]. Yet, despite supra-marginal resections or extended lesionectomies beyond morphological abnormalities, a seizure outcome failure rate of 8-25% still exists[61,68]. Perilesional tissue with focal cortical dysplasia, gliosis, infiltrating tumor residues etc. are often implicated in these surgical failures.

ECoG and the seizure network

Neurons surrounding the LEAT lesion form the epileptogenic zone and thus lesionectomy alone may not guarantee a good seizure outcome. One may argue that if the irritating lesion is removed, the microenvironment may return to normal and the surrounding neurons may cease to discharge abnormally, thereby making ECoG an unnecessary adjunct[61,108,109].

Based on the presumption that neurons surrounding the tumor constitute the epileptogenic zone, removing the tumor alone may not guarantee a good outcome in seizure control[109-111]. However, it can also be argued that if the irritating lesion is removed, the microenvironment may return to normal and the surrounding neurons may cease to discharge abnormally. In pediatric patients, lesionectomy alone yielded very good results. Better results of lesionectomy in children may be due to a shorter history with less opportunity for permanent secondary changes such as hippocampal sclerosis.

The use of ECoG in epilepsy surgery remains controversial[112]. Few studies favor ECoG-guided resections while others have disputed it(Table 5). Few authors advocate its use to assess the 'completeness' of resection. Englot et al in a large meta-analysis of 773 patients with tumor related seizures (100 patients undergoing ECoG) concluded that ECoG offered no significant benefit over lesionectomy alone[96]. Several single-institution retrospective studies have been reported and the long-term benefit of ECoG remains to be convincingly established[109,113-121]. Qui et al reported 87.5% of patients (n = 32) who underwent ECoG guided tailored epilepsy surgery achieved an Engel I score outcome compared to 63.8% of controls (n = 103). The patients' ages ranged from 5 to 66 years with an average age of 37 years. They infer that lesionectomy alone may be sufficient for pediatric patients, whereas adults may benefit more from ECoG[117]. Our study did not find any additional utility for ECoG in children. In our adult cohort too, ECoG was not particularly beneficial to achieve better outcomes.

Bansal et al reported a cohort of pediatric patients with tumor associated epilepsy and showed no correlation between ECoG features and improved outcomes[118]. Kim et al found that gross total resection was a better predictor of seizure freedom than ECoG[112]. In 52 pediatric patients, Wray et al reported that the presence or absence of epileptiform discharges on post resection ECoG was not predictive of seizure freedom[119].

Some papers have suggested amplitude, frequency, or morphology of discharges to be predictive of seizure recurrence, although this has not been found in our study. We agree with studies that suggest that the resection of the entire epileptogenic zone defined by EEG may not be absolutely necessary to achieve seizure freedom. There isn't enough consensus on how to use ECoG to define the epileptogenic zone[112].

Epileptic network in the pediatric domain

Pediatric epilepsy networks have both similarities and differences when compared to those in adults[122,123]. This influences pediatric epilepsy surgery techniques and practices like ECoG guided surgical resections. As epileptic networks are younger and less recrudescent in children, resections beyond the MRI abnormality based on electrical aberrations risking deficits, need a strong justification[112,122]. Epilepsy and neuroplasticity seem to be closely related, as the two processes could positively affect one another. The neuroplastic process has been considered both a cause and consequence of epilepsy, which represents more complexity than only the CNS restructuring.

ECoG vs non-ECoG LEATs- Seizure outcome and adverse events

Tailored epilepsy surgery, rather than lesionectomy, yields better seizure outcome for intracranial neoplasms as suggested by Ogiwara et al., 2010; Tripathi et al., 2010; Voorhies and Cohen-Gadol, 2013[60,101,124]. Guided by intraoperative ECoG, tailored epilepsy surgery targets not only the lesion alone but also the extra or potential epileptogenic foci with abnormal discharges, indicating an aggressive surgical strategy. Although gliosis at the resection site, incomplete resection,

haemorrhage, residual cortical dysplasia, and neuronal injury may contribute to postoperative epileptic seizures, “coexistent pathology” or “dual pathology” at the resection borders are likely causes.

In adults due to tenacious epileptic networks, an isolated lesionectomy may not guarantee a good seizure control outcome. Many studies of paediatric patients reported that lesionectomy alone yielded satisfactory results (Kim et al., 2001; Giulioni et al., 2005)[112]. In adult patients many large series demonstrated that GTR or even extended resection improved seizure prognosis (Awad et al., 1991; Hildebrand et al., 2005; Chang et al., 2008; Englot et al., 2011; Englot et al., 2012; Garcia-Fernandez et al., 2011) [96,112]. It is possible that neoplasms, especially those with long duration, induce secondary epileptogenesis adjacent to or even distant to the primary lesion like secondary hippocampal sclerosis (van Breemen et al., 2007). Better seizure outcome in children may be due to their shorter seizure history, with less opportunity for formation of impregnable epileptic networks. In our series, both pediatric and adult cohorts had similar good outcomes .

Our study also evaluated the post resection ECoG patterns that prompted additional tailored resections and correlated it with the histology of the tailored resection specimen. A post resection 'clean ECoG' and eloquent cortex proximity were the endpoints of the resection. Intermittent non-rhythmic spikes in the resection borders may be distractors, not worth chasing and hence were not followed by extended resections in our study. No additional adverse events related to the tailored resections were noted in our cohort with an acceptable safety profile.

Authors /Year	Age group (Pathology)	No. of patients	Type of study	Good seizure outcome (Engel I)	Mean follow up period	Intraoperative ECoG lesson
Bo Qui, 2014	Both (LEATs)	137	Retrospective	87.7% (ECoG) 63% (No ECoG)	32 months	Better seizure outcome with ECoG
Pei-sen Yao, 2018	Both (LEATs)	108	Prospective	74.07 %	12 months	Useful for tailored resections
Faith C Robertson, 2019	Pediatric (Low grade tumors)	119	Retrospective	80%	5 years	No improved seizure outcome benefit
Greiner, 2016	Pediatric (Tumor,Others)	103	Retrospective	62%	-	Electrographic seizures and frequent spikes on ECoG concordant with seizure onset zone and it's resection
Lesko, 2020	Pediatric (Tumor,Others)	141	Retrospective	78.7%	-	ECoG tailored resections
Hu,2012	Pediatric (Gangliogliomas	55	Retrospective	87.27 %	3.2	No benefit with ECoG

Bansal, 2017	Pediatric (Tumors,Others)	130	Retrospective	80%	2 years	No added benefit with ECoG
Wray, 2012	Pediatric (Tumors,Others)	52	Retrospective	72%	-	Absence of epileptiform discharges on post-ECoG does not appear to predict seizure
Gelinas, 2010	Pediatric	67	Retrospective	80%	1 year	ECoG useful for better outcomes
Englot, 2012	Both (Tumors)	773	Metanalysis	71%	-	Gross total resection more crucial than use of ECoG for better
A.Fallah2015	Pediatric (Tumors)	84	Retrospective	75%	2 years	ECoG useful for planning resections and prognosis
Present study, 2022	Tumors (LEATs)	42	Prospective, Randomised controlled trial.	88.23 %	14 months	No added benefit in seizure outcome

Table 8: Outcomes of ECoG guided resections in different LEATs study.

Relevance of the study for epilepsy surgery in LMIC

About 50 million people suffer from epilepsy worldwide, of whom 80% live in resource limited countries[125,126]. The prevalence of epilepsy in children ranges from 3.2-5.5/1,000 in developed countries and 3.6-44/1,000 in underdeveloped countries. A gross imbalance exists in the availability of epilepsy surgery services with its availability restricted to about 13-21 % of LMIC and nearly 66% of HIC[126-130]. Menon and Radhakrishnan report that only one in 1000 deserving patients receive epilepsy surgery in India[131]. Therefore, the routine and non-judicious use of ECoG with its additional operation time, strain on resources and lack of sufficient supportive evidence is not often justified[131-135]. The other factor that needs to be weighed in is regarding the cost of invasive monitoring and the added burden that it has on the family and institution.

Strengths of the study

The study attempts to generate level I evidence by a randomised trial to evaluate the use of ECoG and to validate its utility in LEATs . Though several retrospective studies and meta-analysis have looked into the utility of ECoG, this study offers more robust evidence from a single centre prospective evaluation. Many studies have addressed the vast spectrum of epileptogenic lesions but the focus on the unique epileptic network in pediatric LEATs is the hallmark of this study. This study may be of value to expand the outreach of epilepsy surgery in the developing world by advocating a judicious use of ECoG thereby making LEATs resections possible in hospitals other than tertiary care centers.

Study Limitations

This is a single-center series and thereby limits its generalisability. A longer duration of follow up would have helped to assess late failures. A correlation of pre-resection ECoG patterns with seizure outcome benefits could be of more value. Impact of ECoG recordings on long term prognostication, cost of care, resource, time utilisation and withdrawal of anticonvulsants are the many aspects unexplored by this study. Being a randomised trial, we had to work on limited number of patients as a pilot study as this was being done as a part of curriculum for post graduate dissertation. We intend to continue this research to include larger number of patients over the next few years whereby we expect to analyse the data over a longer duration of follow up and to explore the social and economic burden of the disease in question.

Despite the limitations, the study firmly asserts the limited role of ECoG in LEATs lesionectomies and therefore advocates its judicious use in resource restricted LMIC.

CONCLUSION

Intra operative ECoG in LEATs resections for patients with anti-seizure medication(ASM) resistant epilepsy does not offer any significant benefit in seizure outcome prognosis or additional surgical planning. Though useful to identify lesional and perilesional inter-ictal electrical activity, this may not have a seizure outcome benefit in LEATs resections. ECoG was not found to be useful for enhancing seizure outcome benefit according to our study. There was no significant difference in its utility in children when compared to adults. Additional tailored resections based on ECoG did not offer any further seizure outcome advantage. Carefully tailored additional resections may not entail more adverse events. Therefore, in resource constrained LMIC epilepsy centres, a balanced and judicious use of ECoG is advocated. Also, the lack of facility to perform IOECoG should not be considered a confounder in undertaking LEATs resection in LMIC epilepsy centers. Hence, epilepsy surgery for LEATs can also be undertaken in centres with limited electrophysiological resources with comparable results.

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ANNEXURES

PROFORMA

Serial No :

Date of Admission :

Date of Surgery :

Date of discharge. :

Handedness :

Seizure descriptions:

Age at onset :

Semiology :

Frequency :

Duration of Epilepsy :

Seizure related disabilities:

AEDs

Past :

Current :

Routine EEG :

Video EEG

Interictal :

Ictal :

Invasive Monitoring

(If available)

Interictal :

Ictal :

Functional Mapping

(if available) :

Neuro Imaging

MRI :

CT :

Any other :

Neuropsychology

IQ score :

Memory score :

Post of risk :

Wada Test

Speech localisation :

Contractual memory support :

Visual Fields

Surgery

Approach :

ECoG assistance :

Intraoperative finding :

Histopathology report :

Post-Operative Imaging :

Postoperative Neurological status

Immediate :

POD 1 :

POD 3 :

3 months :

Post-Operative

Complications

Hematoma**:**

Seizures**:**

Follow up.**:**

Diagnostic Impressions

Seizure classification :

EEG classification :

Epilepsy Classification :

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)
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Institutional Ethics Committee

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

SCT/IEC/1785/DECEMBER/ 2021

14 01 2022

Dr. Sreenath PR
Senior Resident
Department of Neurosurgery
SCTIMST, Thiruvananthapuram

Dear Dr Sreenath,

The Institutional Ethics Committee held on 18th December, 2021, reviewed and discussed your application to conduct the study titled "**INTRA-OPERATIVE ELECTROCORTICOGRAPHY (ECOG) FOR LESIONAL EPILEPSY: A RANDOMISED STUDY** " (IEC/1785).

The following members of the Ethics Committee were present at the meeting held on 18th December, 2021

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1	Prof C.C Kartha	MBBS,MD	Male	Basic Medical Scientist (Chairman)	No
2	Dr Kala Kesavan P	MBBS,MD	Female	Basic Medical Scientist	No
3	Smt Sathi Nair	MA (English Literature)	Female	Lay Person	No
4	Dr Pradeep S	MBBS, MD	Male	Basic Medical Scientist	No
5	Dr. Rejnish Kumar	MBBS,MD ,DNB	Male	Clinician	No
6	Adv Priya Kaimal	LLM MBL	Female	Legal Expert	No
7	Dr Narayanan Namboodiri K K	MBBS MD,DM	Male	Clinician	Yes
8	Dr Manikandan S	MBBS,MD,PDCC	Male	Clinician	Yes
9	Dr Biju Soman	MBBS MD, DPH, MSc, DLSHTM	Male	Basic Medical Scientist	Yes
10	Dr Srinivas G	PhD	Male	Basic Medical Scientist (Member Secretary)	Yes

The following documents were reviewed:

Original submission

1. Covering letter addressed to the Chairperson, IEC, SCTIMST dated 27 08 2021
2. Covering letter addressed to the Chairperson, IEC, SCTIMST dated 28 08 2021 from Dr George C Vilanilam, Additional Professor, Department of Neurosurgery, SCTIMST
3. Checklist Form
4. TAC Approval Letter
5. IEC Application Form
6. Patient Information Form in English and Malayalam
7. Consent Form in English and Malayalam
8. Project Proposal
9. CV of PI and Co-PIs
10. Declaration Form
11. Proforma

Revised submission

1. Covering letter addressed to the Chairperson, IEC, SCTIMST
2. Covering letter addressed to the Chairperson, IEC, SCTIMST dated 28 08 2021 from Dr George C Vilanilam, Additional Professor, Department of Neurosurgery, SCTIMST
3. Checklist Form
4. TAC Approval Letter
5. IEC Application Form
6. Patient Information Form in English and Malayalam
7. Consent Form in English and Malayalam
8. Project Proposal
9. CV of PI and Co-PIs
10. Declaration Form
11. Proforma
12. Assent Form in English and Malayalam

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,

G. Srinivas
Member Secretary, IEC

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES & TECHNOLOGY
INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST
THIRUVANANTHAPURAM

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST, THIRUVANANTHAPURAM

CTRI APPROVAL

CLINICAL TRIALS REGISTRY - INDIA
ICMR - National Institute of Medical Statistics

PDF of Trial
CTRI Website URL - http://ctri.nic.in

Clinical Trial Details (PDF Generation Date :- Sun, 20 Mar 2022 02:49:03 GMT)

CTRI Number	CTRI/2022/03/041067 [Registered on: 14/03/2022] - **Trial Registered Prospectively**
Last Modified On	12/03/2022
Post Graduate Thesis	Yes
Type of Trial	Interventional
Type of Study	Surgical/Anesthesia
Study Design	Randomized, Parallel Group Trial
Public Title of Study	Utility of Intra-operative Electrocorticography (ECoG) in lesional epilepsy surgery
Scientific Title of Study	Intra-operative Electrocorticography (ECoG) in lesional epilepsy- A Randomised study

Secondary IDs if Any

Secondary ID	Identifier
NIL	NIL

Details of Principal Investigator or overall Trial Coordinator (multi-center study)

Details of Principal Investigator	
Name	Sreenath P R
Designation	Senior Resident
Affiliation	Sree Chitra Tirunal Institute for Medical Sciences and Technology
Address	Dept of Neurosurgery Sree Chitra Tirunal Institute for Medical Sciences and Technology Medical College Campus Trivandrum No: 24, Old PG Quarters SCTIMST Staff Quarters Kumarapuram Trivandrum Thiruvananthapuram KERALA 695011 India
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Details Contact Person (Scientific Query)

Details Contact Person (Scientific Query)	
Name	George C Vilanilam
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Source of Monetary or Material Support

Source of Monetary or Material Support
> Sree Chitra Tirunal Institute for Medical Sciences and Technology

Primary Sponsor

Primary Sponsor Details	
Name	Dr Sreenath P R
Address	Dept of Neurosurgery Sree Chitra Tirunal Institute for Medical Sciences and Technology Trivandrum
Type of Sponsor	Other []

Details of Secondary Sponsor

Name	Address
NIL	NIL

Countries of Recruitment

List of Countries
India

Sites of Study

Name of Principal Investigator	Name of Site	Site Address	Phone/Fax/Email
George C Vilanilam	Sree Chitra Tirunal Institute for Medical Sciences and Technology	Department of Neurosurgery SCTIMST, Medical College Campus Trivandrum Thiruvananthapuram KERALA	9567663002 gvil99@yahoo.com

Details of Ethics Committee

Name of Committee	Approval Status	Date of Approval	Is Independent Ethics Committee?
IEC, SCTIMST	Approved	14/01/2022	No

Regulatory Clearance Status from DCGI

Status	Date
Not Applicable	No Date Specified

Health Condition / Problems Studied

Health Type	Condition
Patients	Disorder of central nervous system, unspecified
Patients	Other specified disorders of brain

Intervention / Comparator Agent

Type	Name	Details
Intervention	Electrocorticography	Intra-operative Electrocorticography guided resection of lesional epilepsy during surgery as a one time event
Comparator Agent	Without Electrocorticography	Resection of Lesional epilepsy without intra-operative Electrocorticography assistance during surgery as a one time event.

Inclusion Criteria

Inclusion Criteria	
Age From	2.00 Year(s)
Age To	75.00 Year(s)
Gender	Both
Details	Patients diagnosed with Long term Epilepsy Associated tumors (LEATS) with drug resistant epilepsy who have completed

	pre-surgical work up in SCTIMST under department of Neurosurgery.

Exclusion Criteria

Exclusion Criteria	
Details	Patients undergoing redo surgery, patients with failed surgical outcome and lesions in the eloquent cortex.

Method of Generating Random Sequence	Computer generated randomization
Method of Concealment	On-site computer system
Blinding/Masking	Participant and Outcome Assessor Blinded

Primary Outcome

Outcome	Timepoints
To evaluate if ECoG is useful in lesional epilepsy	Post operative day 1,3 and 90 days

Secondary Outcome

Outcome	Timepoints
To evaluate for standardisation and protocol for recording of ECoG	Post operative day 1, 3 and 90

Target Sample Size	**Total Sample Size=**80 **Sample Size from India=**80 **Final Enrollment numbers achieved (Total)=**Applicable only for Completed/Terminated trials **Final Enrollment numbers achieved (India)=**Applicable only for Completed/Terminated trials
Phase of Trial	Phase 1
Date of First Enrollment (India)	01/04/2022
Date of First Enrollment (Global)	No Date Specified
Estimated Duration of Trial	**Years=**0 **Months=**10 **Days=**0
Recruitment Status of Trial (Global)	Not Applicable
Recruitment Status of Trial (India)	Not Yet Recruiting
Publication Details	Nil
Brief Summary	About 25-30 % of patients with epilepsy are medically refractory and need a pre-surgical work up to assess surgical candidacy. During surgical resections for epilepsy,acute intra-operative electrocorticography (ECoG) is used to record electrical activity from the surgically exposed cortical surface. It is proposed to have additional utility in guiding the extent of surgical resection of the 'ictal onset zone'. The alternate view on ECoG overestimating the ictal onset zone based on less meaningful inter-ictal electrical activity, leading to over-resections,also holds merit.The added costs,expertise and time for ECoG are also matters of concern. Use of ECoG in patients with structural lesions like LEATS(Long term epilepsy associated tumors) remains less explored3.This study therefore aims to develop class 1 evidence to evaluate the utility of ECoG in lesional epilepsy, with a randomized evaluation.

CASE ILLUSTRATION

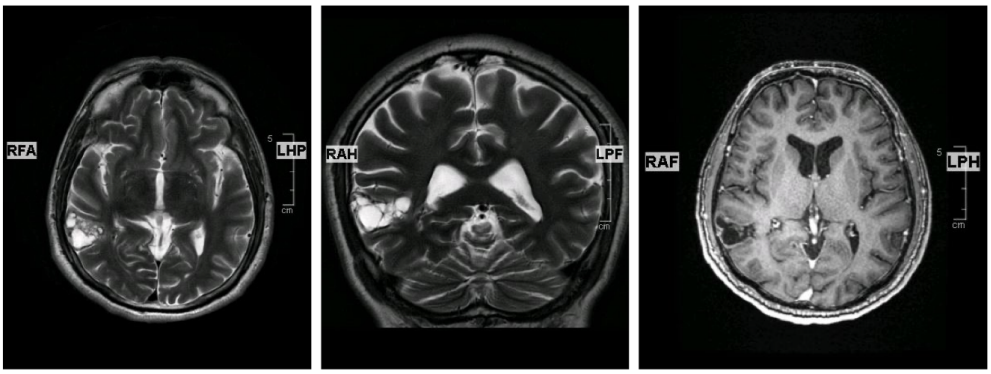

Figure 9. Pre-operative imaging of a 16-year-old boy with right posterior temporal ganglioglioma.

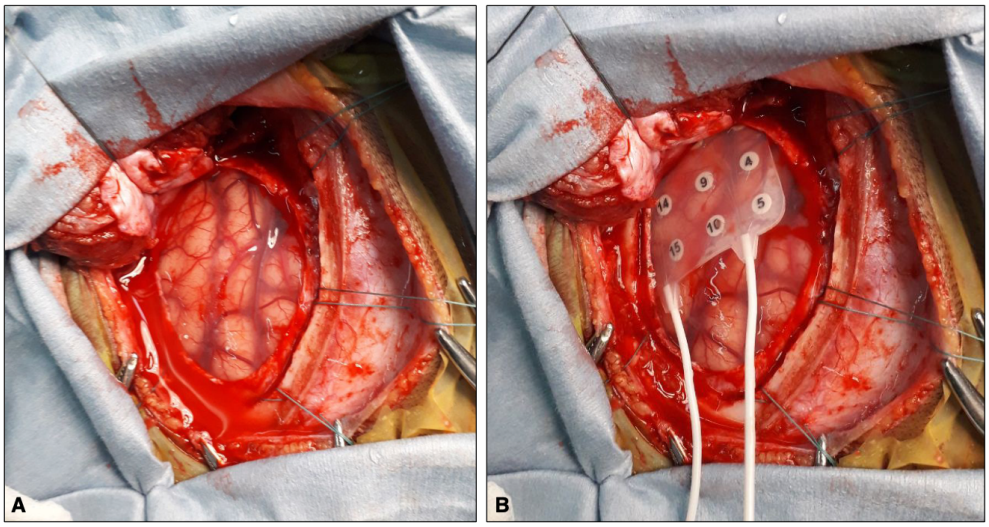

Figure 10. Intra-operative images during a Left Temporal craniotomy and lesionectomy for Left posterior temporal Ganglioglioma. A, following dural opening. B, Placement of pre-resection grid electrodes are shown over the temporal cortex for ECoG recording.

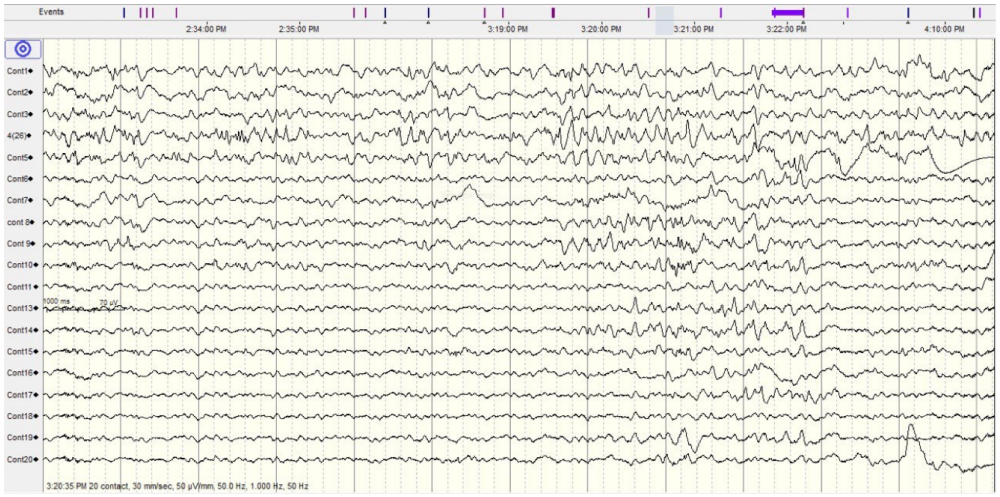

Figure 11. Pre-resection ECoG recording from 16-year-old male with right posterior temporal Ganglioglioma

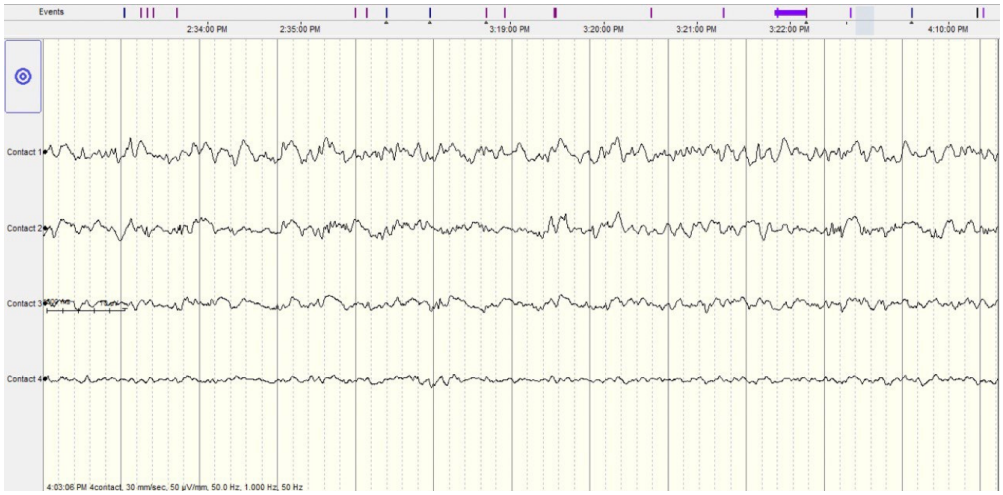

Figure 12. Post-resection ECoG recording from the same patient showing reduction in interictal spikes following resection.

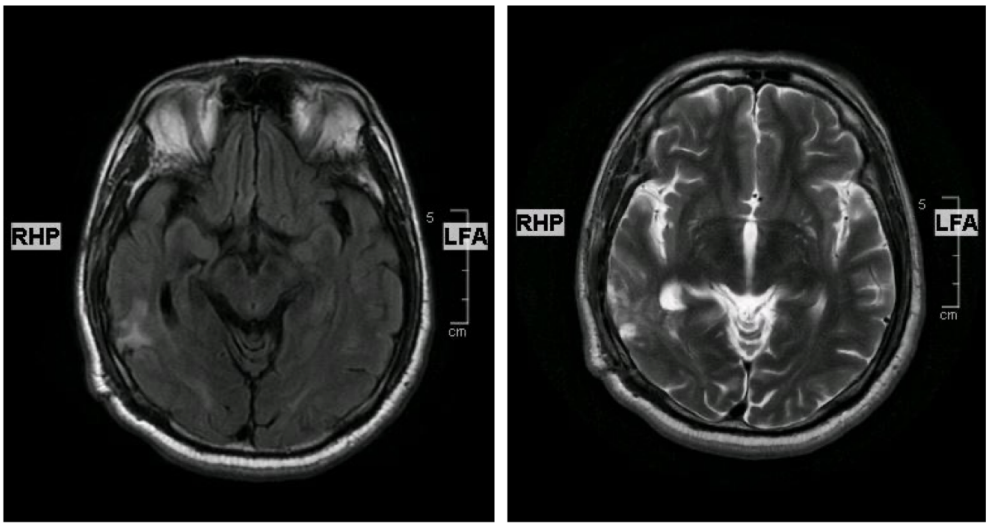

Figure 13. Post-operative imaging of the same patient with complete resection.

HISTOPATHOLOGY

1. GANGLIOGLIOMA

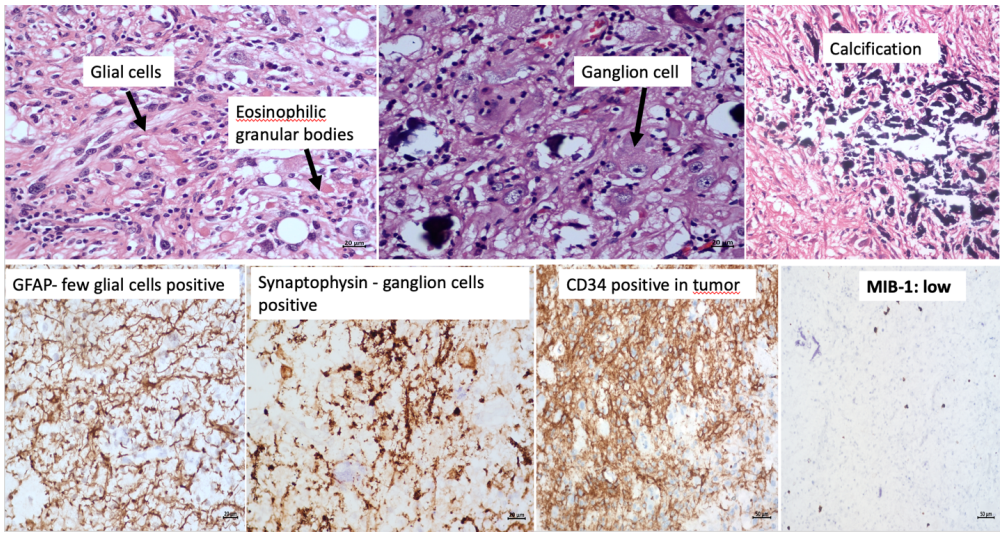

Figure 14. Histopathological images of a case of Ganglioglioma. A; Hematoxylin and Eosin staining showing eosinophilic granular bodies, ganglion cell and areas of calcification. B; Immunohistochemical staining showing special stains like GFAP, Synaptophysin, CD34 and MIB staining.

2. DNET

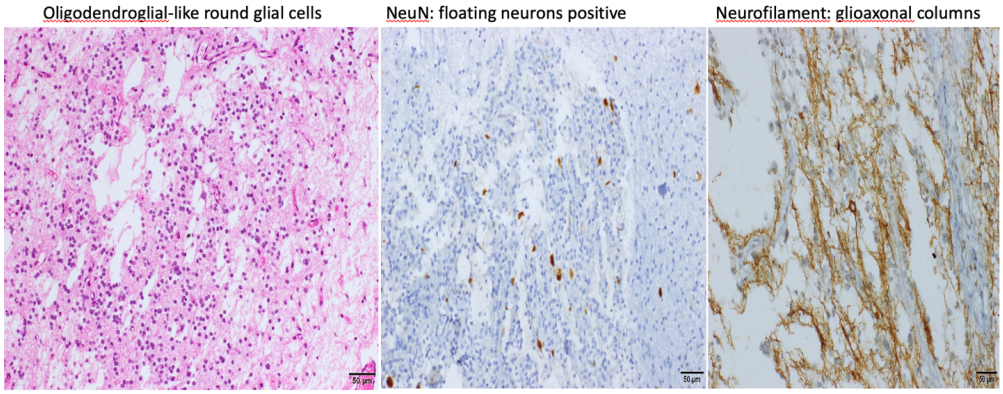

Figure 15. Histopathological images of a case of DNET. A; Hematoxylin and Eosin staining showing round glial cells. B; Immunohistochemical staining with NeuN and Neurofilament.

DATASHEET- NON ECoG COHORT

No	MR No	Age	Sex	Diagnosis	Location	DOA	DOS	DOD	LOS	CC. 1-Seizur	Duration of Symptoms	Associated sy	No of AEDs	AEDs	Cranial Nerv	Motor	Sensory	Cerebellar	MRI Location	Size	Volume
1	479498	13	M	Left medial temporal DNET	2	02/03/20	04/03/20	12/03/20	26	10	1	1	0	1 CBZ 400 BD	0	0	0	0	0 Left PHG and inferior temporal gyrus	46x37x31	49321
4	443662	4	M	Left medial temporal lobe GG/DNET	2	01/03/21	04/03/21	07/03/21	14	6	1	3	0	2 CBZ 300 BD	0	0	0	0	0 Left medial temporal lobe	13x23x14	4186
5	489511	12	F	Left Temporal lobe GG	2	23/03/21	29/03/21	31/03/21	14	8	1	7	0	3 OXC 450 BD	0	0	0	0	0 Left middle and inferior temporal gyrus	41x35x40	57400
7	483986	11	M	Left temporo-occipital glioma	2	18/06/20	22/06/20	25/06/20	23	7	1	1	0	1 LVP 300 BD	0	0	0	0	0 Left occipito-temporal region	35x40x30	42000
10	491568	13	M	Right temporo fronto insular Glioneu	2	01/11/21	13/1/20201	18/1/2021	16	17	1	8	0	4 CBZ 400+TP	0	0	0	0	0 Right insula with fronto temporal extensior	74x89x70	461020
11	480062	2	F	Right fronto temporal lesion	2	23/03/21	26/3/2021	04/01/21	16	11	1	0.5	0	1 LVP 1.5ml BI	0	0	0	0	0 Right frontal lesion	86x73x76	477128
12	505566	13	F	Left Frontal GG	1	29/10/2021	11/03/21	30/11/2021	6	28	2	0.5	2	1 LVP 500 BD	0	0	0	0	0 Left Thalamus	44x40x40	70400
13	496445	10	F	Left Occipital ganglioglioma	4	17/5/2021	21/05/21	25/05/2021	12	8	1	3	0	2 EPT 1-0-2 + F	0	0	0	0	0 Left occipital lobe	34x25x25	21250
2	484027	26	F	Left posterior temporal Ganglioglioma	2	08/07/20	16/07/20	21/07/20	22	13	1	3	0	3 CBZ 400 BD	0	0	0	0	0 Left Occipito-temporal gyrus	26x25x20	13000
4	486060	21	M	Left Parietal GG	3	08/09/20	14/09/20	16/09/20	20	8	1	1	0	2 LVP 500 BD	0	0	0	0	0 Left post central gyrus	22x17x15	5610
5	467009	23	M	Right Frontal DNET/GG	1	03/08/20	11/08/20	13/08/20	21	10	1	1.5	0	2 LVP 750 BD	0	0	0	1	0 Right middle frontal gyrus	13x11x14	2002
7	489577	28	M	Left Temporal DNET	2	25/01/21	03/02/21	05/02/21	15	11	1	0.5	0	2 FRI 5-0-10 +	0	0	0	0	0 Left inferior temporal gyrus	10x11x07	770
9	480647	24	M	Left frontal GG/DNET	1	26/04/21	29/04/21	01/05/21	12	5	1	12	0	2 CBZ 300-0-4	0	0	0	0	0 Left inferior frontal gyrus	19x23x18	7866
11	415935	31	M	Right Parieto-temporal lesion	3	30/12/19	06/01/20	16/01/20	22	17	1	4	2	1 LVP 500 BD	0	0	0	0	0 Right parieto temporal region	47x40x50	94000
15	489231	26	F	Right SFG	1	08/03/21	16/03/21	05/04/21	13	21	1	1.5	0	3 LVP 1g + OXC	0	0	0	0	0 Right SFG	30x26x25	19500
17	472972	19	M	Right temporo-parietal glioma	2	30/12/19	06/01/20	16/01/20	20	17	2	3	1	1 EPT 100 BD	0	0	0	0	0 Right posterior temporo-perisylvian region	54x49x38	100548
20	361913	35	F	Right Occipital Ganglioglioma	4	09/01/21	09/07/21	13/9/2021	8	5	1	13	0	1 VALPR 200 B	0	0	0	0	0 Right occipital lobe	30x23x20	13800
22	318446	26	M	Left frontal DNET	1	22/11/2021	30/11/2021	12/03/21	14	20	1	6	0	2 EPT 100 1-0-	0	0	0	0	0 Left basifrontal	23x27x27	16767
23	284247	59	F	Left Temporal lobeGG	2	04/01/22	12/01/22	14/01/22	4	10	1	14	0	1 CBZ 200 1-0-	0	0	0	0	0 Left temporal lobe	26x18x20	9360

No	Surgery Approach	ECoG assista	HPR 1-GG. 2- DNET.	Associated P	Extended Le	Post-op CT 0-Normal. 1-	Post op seizures Immediate	POD1	POD3	3 months	Post-op complications Hematoma/I	VAVF	Post op imag	No of AEDs pre op	No of AEDs	AEDs at 3 months	AEDs	Engel score
1	Left TPO Craniotomy and Extended lesionectomy	0	2	0	0	0	0	0	0	0	0	1	0	1	1	1	CBZ 400 BD	Ib
4	Left Temporal craniotomy ATL+AH and lesionectomy	0	1	0	0	0	0	0	0	0	1	0	0	2	2	0	CBZ 250 BD -	Ia
5	Left Temporal Craniotomy and Decompression	0	1	0	0	1	0	0	0	0	1	0	0	3	3	3	OXC 450 BD	Ia
7	Left Temporo-occipital craniotomy and gross total excision	0	1	0	0	0	0	0	0	0	0	0	0	1	1	0	LVP 300 BD	Ia
10	Right fronto-temporal craniotomy and subtotal decompression	0	2	0	0	0	1	1	0	0	0	0	1	4	4	3	II	
11	Right fronto-temporal craniotomy and gross total decompressior	0	2	0	0	0	0	0	0	0	0	0	1	1	1	1	LVP 1.5ml BI	Ia
12	Pericoronal parasagittal craniotomy and interhmispheric near to	0	1	0	0	3	0	0	0	0	4	0	1	1	1	1	LVP 500 BD	Ia
13	Left occipital craniotomy and decompression	0	1	0	0	0	0	0	0	0	0	0	1	2	2	2	EPT 1-0-2 + F	Ia
2	Left TP Craniotomy and GTD	0	1	0	0	0	0	0	0	0	0	0	0	3	3	2	CBZ 400 BD	Ib
4	Left Parietal craniotomy and Excision	0	1	0	0	0	0	0	0	0	0	0	0	2	2	1	LVP 500 BD	Ia
5	Right Frontal Craniotomy and Decompression	0	1	0	0	0	0	0	0	0	0	0	0	2	3	0	LVP 500 BD	Ia
7	Left posterior temporal craniotomy and excision	0	1	0	0	0	0	0	0	0	0	0	0	2	2	2	FRI 5-0-10 +	Ia
9	Left Fronto-temporal craniotomy and Decompression	0	2	0	0	0	0	0	0	0	0	0	0	2	2	2	CBZ 300-0-4	Ia
11	Right Parieto-temporal craniotomy and gross total excision	0	1	0	0	0	0	0	0	0	0	0	0	1	1	1	LVP 250 BD	Ib
15	Pericoronal parasagittal craniotomy and contralateral transfalcir	0	1	0	0	0	1	0	0	0	0	0	0	3	3	3	OXC 600 BD	Ia
17	Right temporo-parietal craniotomy and Gross total excision	0	1	0	0	0	0	0	0	0	0	0	0	1	1	1	EPT 100 BD	Ia
20	Right occipital craniotomy and gross total excision	0	1	0	0	0	0	0	0	0	0	0	0	1	1	1	LVP 250-0-5	Ia
22	Left pterional craniotomy and excision	0	2	0	0	0	0	0	0	0	5	0	0	2	2	2	EPT 100 1-0-	Ia
23	Left temporal craniotomy and gross total excision	0	1	0	0	0	0	0	0	0	5	0	0	1	1	1	CBZ 200 1-0-	Ia

DATASHEET- ECoG COHORT

No	MR No	Age	Sex	ECoG Assista	Diagnosis	Location	DOA	DOS	DOD	LOS	Follow up di	CC. 1-Seizure	Duration of Sym	Associated s	No of AEDs	AEDs	Cranial Nerv	Motor	Sensory	Cerebellar	MRI Location	Size	Volume
2	485479	4	M		1 Left Medial temporal GG		2	02/12/20	07/12/20	10/12/20	17	8	1	1	0	2 OXC 150 BD + F	0	0	0	0	0 Left medial temporal lobe	15x15x15	3375
3	462316	16	M		1 Left medial temporal GG		2	25/01/21	27/01/21	02/02/21	15	8	1	14	0	3 OXC 600 HS + F	0	0	0	0	0 Left medial temporal lobe	12x10x8	960
6	496885	15	M		1 Left Parieto-occipital DNET		3	03/05/21	04/05/21	07/05/21	12	4	1	1	0	1 LVP 500 BD	0	0	0	0	0 Left para central lobule	40x30x70	84000
8	494703	14	M		1 Left anterior temporal GG		2	30/07/21	08/03/21	09/08/21	9	9	1	6	0	4 OXC 600 BD + L	0	0	0	0	0 Left anterior temporal lob	15x8x10	1200
9	486241	15	M		1 Left medial temporal DNET		2	10/10/21	19/10/2020	29/10/21	19	10	1	1	0	1 LVP 500 BD	0	0	0	0	0 Left medial temporal lobe	37x26x35	33670
14	497029	8	M		1 Left Occipital GG		4	07/06/21	14/06/21	16/06/21	11	9	1	4	0	1 LVP 300 BD	0	0	0	0	0 Left occipital lobe	44x30x32	42240
15	437281	6	M		1 Left Frontal DNET		1	22/6/2021	24/6/2021	28/6/2021	11	6	1	5	0	2 OXC 400 BD + F	0	0	0	0	0 Left superior frontal gyrus	68x42x41	117096
16	439686	18	M		1 Right medial Temporal GG		2	23/07/21	26/07/21	02/08/21	9	9	1	17.5	0	4 LVP 1.5g + VNL 1g	0	0	0	0	0 Right medial temporal lob	15x20x10	3000
17	496623	15	F		1 Right Temporal ganglioglioma		2	28/07/21	16/04/21	02/08/21	4	7	1	2	0	4 OXC 450 Inj, BD	0	0	0	0	0 Right posterior temporal	26x20x15	13520
1	296215	21	F		1 Right Frontal DNET		1	21/07/20	30/07/20	03/08/20	21	13	1	14	0	2 CBZ 400 BD + F	0	0	0	0	0 Right Frontal cortex	26x20x19	9880
3	296707	38	M		1 Right Temporal polar DNET with FCD		2	16/07/20	17/07/20	27/07/20	22	11	1	18	0	2 OXC 600 BD + F	0	0	0	0	0 Right Temporo polar	18x14x19	4788
6	467668	40	F		1 Left Temporal DNET		2	19/12/20	21/12/20	24/12/20	17	6	1	26	0	1 CBZ 400 BD	0	0	0	0	0 Left posterior inferior tem	12x13x14	2184
8	477731	21	M		1 Right Parieto-occipital DNET		3	09/02/21	12/02/21	17/02/21	15	8	1	13	0	2 PHB 60 BD + EP	0	0	0	0	0 right parieto-occipital reg	23x25x21	11550
10	475926	35	F		1 Right Orbito-frontal GG		1	07/09/20	11/09/20	21/09/20	20	14	1	20	0	2 CBZ 600 + LVP	0	0	0	0	0 Right basifrontal lobe	28x25x20	14000
12	456198	28	F		1 Right medial temporal Ganglioglioma		2	16/02/20	17/02/20	22/02/20	22	6	1	15	0	3 OXC 600BD + TI	0	0	0	0	0 Right mesial temporal lob	20x15x25	7500
13	466616	37	M		1 Right medial temporal Ganglioglioma		2	17/02/20	25/02/20	02/03/20	22	13	1	2	0	1 LVP 500 BD	0	0	0	0	0 Right mesial temporal lob	24x21x30	15120
14	246182	31	F		1 Right temporal FCD		2	01/11/20	05/11/20	10/11/20	18	10	1	20	0	1 LVP 500 BD	0	0	0	0	0 Right temporal lobe	28x25x25	17500
16	473461	31	M		1 Left MTL with secondary hippocampal sc		2	13/04/21	16/04/21	23/04/21	13	10	1	16	0	3 LVP 1.5g + OXC	0	0	0	0	0 Left mesial temporal lobe	15x15x12	3375
18	436355	46	M		1 Right posterior temporal GG		2	13/09/21	20/9/2021	24/09/21	8	11	1	29	0	2 FRI 10 HS + OXC	0	0	0	0	0 Right temporal cortex	28x30x22	18480
19	490941	24	M		1 Left temporal glioneuronal tumor		2	16/11/21	17/11/2021	25/11/21	6	9	1	8	0	2 LAM 300 + CLB	0	0	2	0	0 Left inferior temporal gyri	10x10x10	1000
21	475512	20	M		1 Right frontal opercular GG		1	02/12/21	03/12/21	08/12/21	5	6	1	6	0	4 OXC 1.2g + CLB	0	0	0	0	0 Right frontal operculum	18x14x16	4032
24	497457	27	F		1 Left Occipital GG		4	18/04/22	19/04/22	21/04/22	4	8	1	7	0	2 LAC 150 BD + F	0	0	0	0	0 Left Occipital lobe	25x20x25	12500
25	495854	21	M		1 Right temporal DNET		2	28/03/22	29/03/22	05/04/22	4	12	1	3.5	0	2 OXC 1.2g + CLB	0	0	0	0	0 Right temporal lobe	36x26x23	21528

No	Surgery Approach	ECoG assistai HPR 1- GG, 2- DNI	Associated P. 0- None, 1- FCD	Extended Les	Post-op CT 0-Normal, 1-	Post op seizures Immediate	POD1	POD3	No of AEDs 3 months	AEDs	Post-op complications Hematoma/f	VAVF	Post op imag	No of AEDs pre op	No of AEDs	AEDs at 3 months	Engel score
2	Left Temporal craniotomy ATL+AH and lesionectomy	1	1	0	0	0	0	0	0	0	0	0	2	2	2	1	1 Ia
3	Left Temporal craniotomy and ATL+AH and Lesionectomy	1	1	0	1	0	0	0	0	5	1	0	3	3	3	3	3 Ia
6	Left Occipital Craniotomy and Excision	1	1	0	0	0	0	0	0	0	0	0	1	1	1	1	1 Ia
8	Left anterior temporal lobectomy+ lesionectomy and AH	1	1	0	0	0	0	0	0	0	0	0	4	4	4	4	4 Ia
9	Left ATL+AH and Uncusectomy and Gross total excision	1	2	0	0	0	0	0	0	0	0	0	1	1	1	1	0 Ia
14	Left parieto-occipital craniotomy and extended lesionectomy	1	1	0	1	0	0	0	0	0	0	0	1	1	1	1	1 Ia
15	Left post coronal parasagittal craniotomy and gross total decompressi	1	2	0	1	0	0	0	0	5	0	0	2	1	1	1	1 Ia
16	Right Temporal Craniotomy and lesionectomy and ATL+AH	1	1	0	0	1	0	0	0	6	0	0	4	4	4	3	3 Ia
17	Right Temporal craniotomy ATP and Gross total excision	1	3	0	0	0	0	0	0	0	0	0	2	2	2	2	2 Ia
1	Right Postcoronal parasagittal awake craniotomy and GTE	1	2	0	0	0	0	0	0	0	0	0	2	2	2	2	2 Ia
3	Right Temporal Craniotomy and lesionectomy and ATL+AH	1	1	0	0	1	0	0	0	0	0	0	2	3	3	3	3 Ia
6	Left Temporal craniotomy and extended lesionectomy	1	2	0	1	0	0	0	0	0	0	0	1	1	1	1	1 Ia
8	Left temporal craniotomy ATL+AH and Lesionectomy	1	2	0	0	0	0	0	0	5	1	1	2	2	2	2	2 Ia
10	Right Fronto-temporal Craniotomy + ATL and Total excision	1	1	0	0	0	0	0	0	0	0	2	2	2	2	2	2 Ib
12	Right Temporal craniotomy and ATL+AH	1	1	0	0	0	0	0	0	0	0	0	3	3	3	3	3 Ia
13	Right temporal craniotomy and ATL+AH and Extended lesionectomy	1	1	0	1	0	0	0	0	0	0	0	1	1	1	1	0 Ia
14	Right temporal craniotomy and anterior temporal lobectomy	1	1	0	0	0	0	0	0	0	0	0	3	3	3	3	3 Ic
16	Left ATL+AH and gross total excision of left mesial temporal lesion	1	1	0	0	0	0	0	0	0	1	0	3	3	3	3	3 Ia
18	Right Temporal craniotomy and gross total excision	1	1	0	0	0	0	0	0	0	0	1	2	2	2	2	2 Ia
19	Left temporal craniotomy and gross total excision	1	1	0	1	0	0	0	0	0	0	0	2	2	2	2	2 Ia
21	Right pterional craniotomy and excision	1	1	0	0	0	0	0	0	0	0	0	4	4	4	3	3 Ia
24	Left Occipital craniotomy and gross total excision	1	1	0	0	0	0	0	0	0	0	0	2	2	2	2	2 Ia
25	Right Temporal Craniotomy and lesionectomy and ATL+AH	1	1	0	0	0	0	0	0	2	0	0	2	2	2	2	2 Ia