POST SURGICAL OUTCOME OF LONG TERM EPILEPSY ASSOCIATED TUMORS (LEAT): A RETROSPECTIVE COHORT STUDY

THESIS

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CERTIFICATE

This is to certify that the work incorporated in this thesis titled

"POST SURGICAL OUTCOME OF LONG TERM EPILEPSY ASSOCIATED TUMORS (LEAT): A RETROSPECTIVE COHORT STUDY"

for the degree of

M.Ch NEUROSURGERY

has been carried out by DR. PRADEEPANAND VAIDYA

under my supervision and guidance. The work done in connection with this thesis has been carried out by the candidate himself and is genuine.

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DECLARATION

This thesis titled "**Post Surgical Outcome of Long Term Epilepsy Associated Tumors (LEAT): A Retrospective Cohort Study**" is a consolidated report based on a bonafide study of the period from January 1998 to December 2016, done by me under the Department of Neurosurgery, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram.

This thesis is submitted to SCTIMST in partial fulfillment of rules and regulations of M.Ch Neurosurgery examination.

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INTRODUCTION

The term long-term epilepsy associated tumor (LEAT) encompasses lesions identified in patients investigated for long histories (often 2 years or more) of drug-resistant epilepsy. The concept of "long-term epilepsy associated tumor (LEAT)" was introduced by Luyken et al. (2003)[1] They are generally slowly growing, low grade, cortically based tumors, more often arising in younger age groups and in many cases exhibit neuronal in addition to glial differentiation. In studies which analyzed the pathologic findings in patients with drug resistant partial epilepsy, tumors constituted approximately 25–35% of the cases[2]. The incidence of epilepsy in these tumors varies between 30 and 100% and depends on the tumor type, with dysembryoplastic neuroepithelial tumor (DNETs) being the most epileptogenic (100%)[3]. LEATs are further united by cyto-architectural changes that may be present in the adjacent cortex which have some similarities to developmental focal cortical dysplasias (FCD); these are now grouped as FCD type IIIb in the updated International League Against Epilepsy (ILAE) classification. Epilepsy associated with LEAT is generally poorly controlled by antiepileptic drugs while, on the other hand, it is high responsive to surgical treatment. However the best management strategy of tumor-related focal epilepsies remains controversial representing a contemporary issues in epilepsy surgery.By using an epilepsy surgery oriented strategy LEAT may have an excellent seizure outcome therefore surgical treatment should be offered early, irrespective of pharmacoresistance, avoiding both the

consequences of uncontrolled seizures as well as the side effects of prolonged pharmacological therapy and the rare risk of malignant transformation[4] Intractable epilepsy has major and diverse medical, psychological and social consequences, such as therapeutic dependence, side effects of anti-epileptic drugs, behavioural changes, loss of independence, and interference in work and leisure activities. Hence it critically affects the daily quality of life of patients with a brain tumours even if the tumour itself is under control.

There is present need for development of comprehensive epilepsy program including multidisciplinary team including dedicated neurologists, neurosurgeon, psychologists, and radiologists to understand the disease from feasibility of surgical point of view. Tripathi M et al feels that there is need for national epilepsy control program in developing countries like India. The combined efforts of the team are essential to identify the best surgical candidate and improving results in form of seizure outcome and reducing the peri-operative complication. Sree Chitra Tirunal Institute of Medical Sciences and Technology is one of the pioneers in epilepsy care and have center for comprehensive epilepsy care which is offering such treatment options by combined efforts of various disciplines needed. In past and present various surgical procedure are being done for refractory epilepsy according to patient requirement.

AIMS AND OBJECTIVES

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Hypothesis:

Completeness of lesion resection in Long Term Epilepsy associated tumors (LEAT) is associated with a good seizure and quality of life outcome.

AIM : To study the post operative outcome of Long Term Epilepsy associated tumors (LEAT)

PRIMARY OBJECTIVE:

Measurement of seizure outcome status

SECONDARY OBJECTIVE:

To study the factors affecting the outcome like duration of epilepsy ,electrophysiological correlation, completeness of resection, and time taken for reduction of anti convulsants after surgery.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

In 1882, the neurologist Hughlings Jackson described the important observation that seizures often represent a first and unique clinical manifestation of glial tumours . Every fourth patient submitted to epilepsy surgery suffers from a brain tumor .Epilepsy associated-tumor is a debilitating condition, causing distress and adversely affecting the quality of life[1]. Microscopically, these

neoplasms present with a wide-ranging spectrum of glial or glio-neuronal tumor subtypes. Gangliogliomas (GG) and dysembryoplastic neuroepithelial tumors (DNETs) are the most frequently recognized entities accounting for 65 % of 1,551 tumors collected at the European Epilepsy Brain Bank (*n* = 5,842 epilepsy surgery samples). These tumors often present with early seizure onset at a mean age of 16.5 years, with 77 % of neoplasms affecting the temporal lobe. Relapse and malignant progression are rare events in this particular group of brain tumors. Surgical resection should be regarded, therefore, also as important treatment strategy to prevent epilepsy progression as well as seizure and medication-related comorbidities.

The characteristic clinical presentation and broad histopathological spectrum of these highly epileptogenic brain tumors was classified as "long-term epilepsy associated tumors—LEATs"[5]. LEATs differ from most other brain tumors by early onset of spontaneous seizures, and conceptually are

regarded as developmental tumors to explain their pleomorphic microscopic appearance and frequent association with Focal Cortical Dysplasia Type IIIb. However, the broad neuropathologic spectrum and lack of reliable histopathological signatures make these tumors difficult to classify using the WHO system of brain tumors

Epilepsy associated with brain tumours can be divided into two groups: tumors without other symptoms (usually low-grade tumors affecting children or young patients) or tumors together with neurological deficits (more frequently high-grade tumours in middle-aged and older patients)[6].

Epileptic seizure incidence varies according to tumour location and histotype. Furthermore low-grade tumors often are more epileptogenic than high-grade tumours[5]

In the group of epilepsy associated with low grade tumors it is useful to further distinguish between the pre-eminence of oncological and epileptic logical aspects. In the group of the "diffuse low grade glioma" (LGG) the oncological aspects should prevail according to the progressive course of the neoplastic brain disease[7]. On the contrary in the group of LEAT, mainly represented by glioneuronal tumors (GNTs), epilepsy control should be the main goal[8].

The group of LEAT, is currently enlarging not only for the recognition of new, often rare, histotypes but also for the identification of tumors having hybrid and/or mixed features[9]The biologic behaviour of LEAT is generally

benign even if some tumors could present recurrence or malignant transformation[1]

DEFINITION OF EPILEPSY

In year 2005, ILAE defined epilepsy conceptually as ―a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures.This definition was usually practically applied as having two unprovoked seizures >24 h apart.

The International League Against Epilepsy (ILAE) in 2014 has published accepted recommendations of a task force altering the practical definition for special circumstances that do not meet the two unprovoked seizures criteria. The task force proposed that epilepsy be considered to be a disease of the brain defined by any of the following conditions:

(1) At least two unprovoked (or reflex) seizures occurring >24 h apart;

(2) One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years;

(3) Diagnosis of an epilepsy syndrome.

Epilepsy is considered to be resolved for individuals who either had an age dependent epilepsy syndrome but are now past the applicable age or who have remained seizure-free for the last 10 years and off antiseizure

medicines for at least the last 5 years. Resolved is not necessarily identical to the conventional view of remission or cure.

Epileptic seizures result from an excessive discharge in a population of hyper-excitable neurons. Typically, the seizures are generated in the cortical and hippocampal structures. The clinical manifestation of a seizure depends on its site of origin, time course and discharge outbreak [10]. Focal epileptic seizures are conceptualized as originating within networks limited to one hemisphere and generalized seizures originate at some point within, and rapidly engaging, bilaterally distributed networks[11] . The ILAE´s new "roadmap" for the relevant classification of epilepsies for discussion is presented in Figure 1.

Table 1 represents The International League Against Epilepsy (ILAE) new operational classification of seizure types [12]. Age at onset, cognitive and developmental antecedents and consequences, clinical neurological examination, EEG features, associated structural changes, triggering or provoking factors and patterns of seizure occurrence with respect to sleep all contribute to epileptic syndromes.

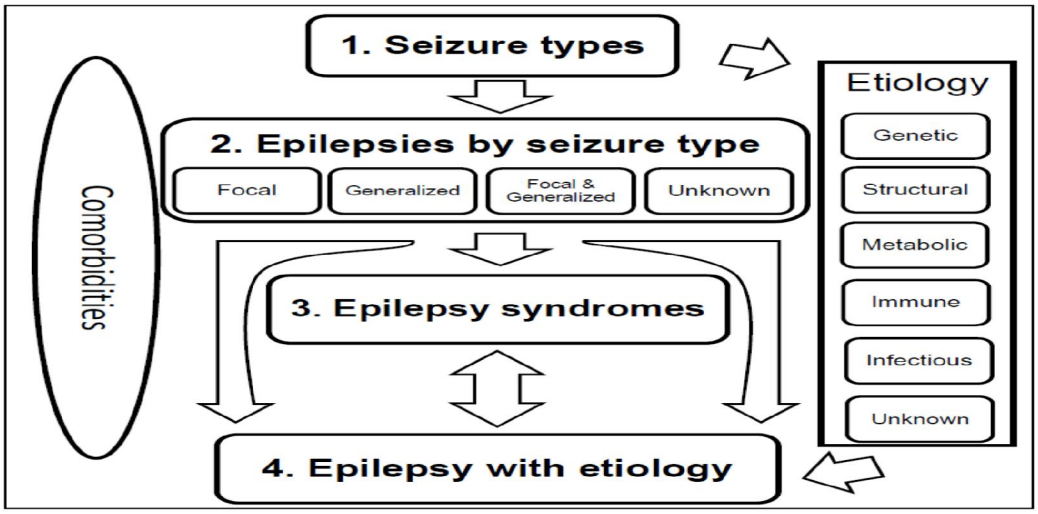

Figure 1:ILEA Roadmap for seizure classification

ILAE 2017 Classification of Seizure Types Expanded Version

Focal Onset

Aware | Impaired Awareness

Motor Onset
- automatisms
- atonic
- clonic
- epileptic spasms
- hyperkinetic
- myoclonic
- tonic

Non-Motor Onset
- autonomic
- behavior arrest
- cognitive
- emotional
- sensory

focal to bilateral tonic-clonic

Generalized Onset

Motor
- tonic-clonic
- clonic
- tonic
- myoclonic
- myoclonic-tonic-clonic
- myoclonic-atonic
- atonic
- epileptic spasms

Non-Motor (absence)
- typical
- atypical
- myoclonic
- eyelid myoclonia

Unknown Onset

Motor
- tonic-clonic
- epileptic spasms

Non-Motor
- behavior arrest

Unclassified

TABLE 1. The International League Against Epilepsy (ILAE) classification of seizure types

PROBLEM STATEMENT

Epilepsy is an important for public health burden as the most common disabling neurological disorders occurring across the life span. The prevalence of epilepsy is estimated to be about 1% of the U.S. population (Kobao et al.). The World Health Organization reports that more than 100 million people are affected by epilepsy worldwide. Centers for Disease Control and Prevention emphasizes the lack of research on prevalence and incidence and recently stated that epidemiological and surveillance data on epilepsy are limited

French JA et al in their publication states ,because the most important initial steps in effective treatment of epilepsy involve accurate diagnosis and subsequent selection of appropriate antiepileptic drugs based on seizure type, classification of the epilepsy based on precise history and supportive clinical testing is critical for optimal outcome.‖

The spectrum of epilepsy associated neuroepithelial tumours

Summary of tumours collected in adults and children at the German Neuropathology Reference Center for Epilepsy Surgery in Erlangen.(Table 2)states that more than 80% of tumours present with seizure onset before age of 15 years (upper 6 rows), and localize in 77% to the temporal lobe, herein designated as low-grade/long term epilepsy-associated neuroepithelial tumours (LEAT). Early seizure onset and temporal

localization separate LEAT from semi-benign and diffusely infiltrating gliomas also encountered in epilepsy surgery series (lower 3 rows).

Entity	Numbers (%)	Onset	Duration	Age OP
ANT I°	5 (0.4%)	**2.0**	13.0	19.7
GG I°	673 (48.7%)	**12.8**	12.7	24.9
GG II°/III°	77 (5.6%)	**14.2**	11.0	26.9
ISO I°	29 (2.1%)	**14.4**	17.7	27.9
DNT I°	256 (18.5%)	**14.7**	10.7	25.2
PA I°	81 (5.9%)	**14.8**	12.1	25.1
PXA II°	38 (2.7%)	*18.8*	12.2	29.3
OLIGO II°/III°	97 (7%)	*24.5*	12.5	38.6
ASTRO II°/III°	110 (8%)	*29.5*	6.7	36.2
Total	***1382***	***16.5***	***11.7***	***27.9***

Table 2:Age at epilepsy onset (mean in years); Epilepsy duration (mean in years); Age at operation (mean in years);

The influence of tumor location

In addition to tumor type, tumor location influences the incidence of epilepsy. For instance, prior groups have noted that tumors located in superficial cortical areas are most likely to be associated with seizures (Penfield et al., 1940; Fried et al., 1994; Liigant et al., 2001; Lynam et al., 2007; Lee et al., 2010), as are lesions centered in the temporal lobe, frontal lobe, or insula (Lund, 1952; Liigant et al., 2001; Zaatreh et al., 2002, 2003; Lynam et al., 2007; Lee et al., 2010). Lee and others (2010) analyzed tumor location in 124 glioma patients with seizures, using a summed statistic image to map aggregate tumor location,The authors noted that gliomas most likely to be associated with seizures were located in the temporal lobe, followed by the frontal lobe. It is likely that the inherent epileptogenicity of structures in the mesial temporal lobe contributes to seizure generation in this region (Delgado-Escueta et al., 1986; Engel et al., 2009). Furthermore,

Spencer and colleagues have described that dual pathology – including gliosis, hippocampal sclerosis, and cortical dysgenesis – may further drive epileptogenesis in tumor related temporal lobe epilepsy (Fish and Spencer, 1995; Spencer and Huh, 2008). Some groups have reported a lower incidence of seizures in *de novo* glioblastomas than those having progressed from known lower-grade gliomas[13], and others have found that seizures may precede radiologic evidence of malignant tumor transformation (Rossi et al., 2010). Finally, epilepsy is reported to be more common in patients with multifocal disease than in those with a solitary tumor[13]

Refractory seizures

There is no single definition for medical refractory epilepsy, although a clinically useful definition is the presence of seizures so frequent or severe that they limit daily life despite the use of antiepileptic drugs and adequate serum concentrations.[14] About 20% of patients with primary generalised epilepsy and 35% of those with partial seizures meet this definition,[14] for whom genetic causes of drug resistance probably play a major part.[15] Refractory epilepsy is commonly associated with a structural brain lesion (including a brain tumour) and with a seizure frequency of 12–50%

Although the concept of drug resistant (often used interchangeably with ‘‘medically refractory/intractable’’ or ‘‘pharmacoresistant’’) epilepsy may appear self-explanatory and intuitive, a precise definition has remained elusive.

This has resulted in diverse criteria used by different clinicians and researchers, or even a lack of explicit criteria in some cases, rendering it difficult to compare findings across studies and to make practice recommendations (Perucca, 1998; Tanganelli & Regesta, 1999; Berg et al., 2006; Kwan & Brodie, 2006; Arzimanoglou & Ryvlin, 2008). In response to this situation, the International League Against Epilepsy (ILAE) appointed a Task Force under the Commission on Therapeutic Strategies to formulate a proposal for a consensus definition of drug resistant epilepsy.

On the basis of a careful deliberation of the available evidence, for operational purposes, the following definition is proposed:

"Drug resistant epilepsy may be defined as failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom".[16]

Mechanism of failure of antiepileptic drugs in patients with brain tumours

Antiepileptic drugs do not control seizures in some patients with brain tumours because of loss of receptor sensitivity. Additionally, multidrug-resistance proteins associated with brain tumours are a major cause of refractoriness. Patients with refractory epilepsy are commonly resistant to many antiepileptic drugs despite different mechanisms of action, which suggests nonspecific mechanisms of resistance.[17] For instance, there might

be overexpression of proteins that belong to the multidrug-resistance pathway. These proteins are

members of the ATP-binding cassette transporter family, which form part of active membrane pumps that facilitate or block the transport of substances over the endothelial cell membrane.[18]

Expression of multidrug-resistance proteins in tumour cells of patients with glioma is high, suggesting that they can diminish drug transport into the brain parenchyma(figure 2).[18]In healthy brains, the multidrug-resistance gene *MDR1(ABCB1*, P-glycoprotein) and multidrug-resistance-related protein (MRP, ABCC1) contribute to the function of the blood‑brain barrier and blood‑cerebrospinal fluid barrier.[19] *MDR1* is expressed in the apical membranes of many barrier tissues such as the intestines, liver, blood‑brain and blood‑cerebrospinal fluid barriers, thus contributing to plasma and cerebrospinal fluid, but also to intracellular drug disposition.

Insufficient concentration of antiepileptic drugs in the blood can be the result of an active defence mechanism by MDR1, which restricts the penetration of lipophilic substances into the brain. Carbamazepine, phenytoin, phenobarbital, lamotrigine and felbamate are substrates for this gene product**.**[17] Research suggests that a non-specific transporter can move gabapentin out of the brain.[20]Breast-cancer-resistance protein (ABCG2) is another member of the ATP-binding cassette transporter family, expression

of which is increased in brain-tumour tissue compared with healthy brain tissue.[21] This protein can transport antiepileptic drugs, and thus might belong to the multidrug-resistance pathway in patients with brain tumours

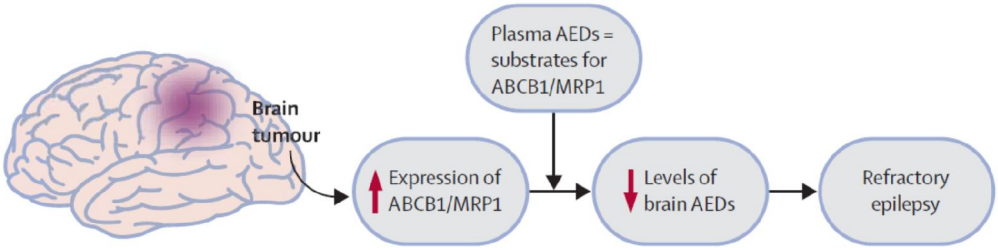

Fig 2:The brain tumour stimulates the expression of multidrug-resistance proteins, which prevent antiepileptic drugs (AEDs) penetrating the brain. Low concentrations of AEDs in the brain parenchyma explain the occurrence of refractory epilepsy in patients with brain tumours

LEATs:

Gangliogliomas

Gangliogliomas are usually benign intra axial neoplasms that were first described by Perkins in 1926. They are composed of dysplastic neurons and neoplastic glial cells. Both cell populations may show heterogeneity, with the morphological spectrum ranging from a predominantly neuronal phenotype to a predominant glial population. Some gangliogliomas may also exhibit clear cell morphology which makes the differential diagnosis of oligodendrogliomas or DNET difficult. However, the immunohistochemical profile of gangliogliomas (e.g., expression of the stem cell epitope CD34) usually allows a specific diagnosis(figure 3).[22]GG can occur in any part of

the central nervous system, although the temporal lobe is the most common location[23] followed by the frontal lobe, the optic pathway, the spinal cord, the brainstem, the cerebellum and the pineal gland.

On MRI, gangliogliomas associated with temporal lobe epilepsy are consistently located in the cortex or in the cortex and subcortical white matter and have a spatial preponderance for the parahippocampal and lateral temporooccipital gyri . The classical imaging features are the combination of intracortical cyst(s), a circumscribed area of cortical (and subcortical) signal increase on FLAIR and T2-weighted images and a contrast enhancing nodule[24] . Calcifications are present in 1/3 of cases(figure 4 [4]). If contrast enhancement is absent (50% of cases), gangliogliomas may be difficult to distinguish from cortical dysplasias. Especially, in these cases intracortical cysts are highly diagnostic. Gangliogliomas typically have no perifocal edema. If edema is present, malignant degeneration (from the glial component) to a WHO grade II or III ganglioglioma or anaplastic glial tumors including PXA with anaplastic features should be suspected.

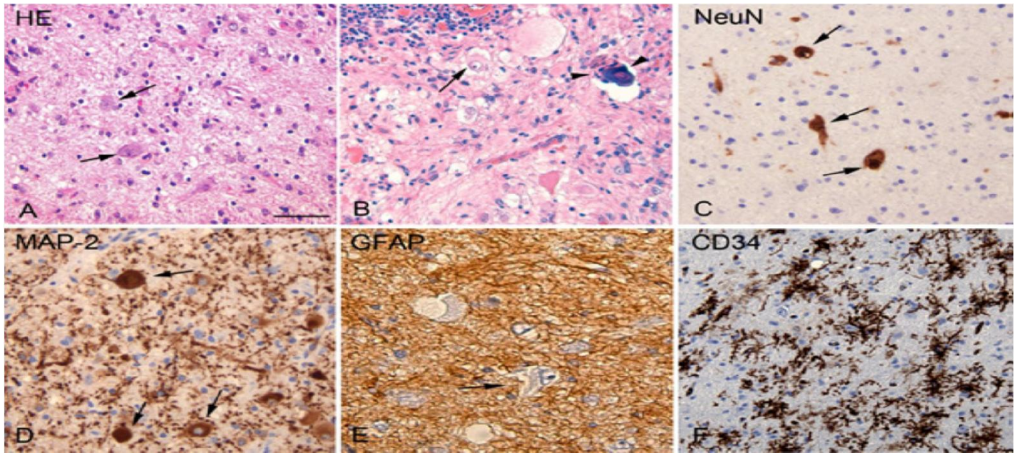

Figure 3:Pathological and immunohistochemical features of GGs. **A**, **B**. Hematoxylin and eosin (HE) staining of GG showing the mixture of neuronal cells (arrows), lacking uniform orientation, glial cells and calcification (arrow-heads). NeuN (**C**; nuclear staining) and MAP-2(**D**) staining detect the neuronal component of GG (arrows). **E**. Glial fibrillary acidic protein (GFAP) showing the astroglial component of GG. **F**. CD34 immunostaining showing expression of stem cell marker within the GG

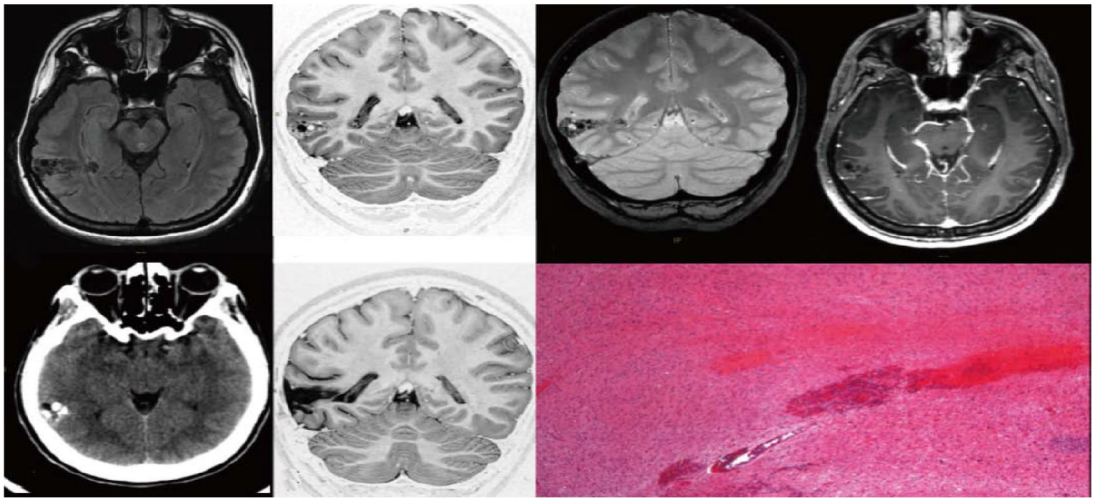

Figure 4:Ganglioglioma World Health Organization grade I of the right posterior middle temporal gyrus. Axial FLAIR T2-w (A) and coronal IR T1-w (B) images show inhomogeneous cortical-subcortical mass extending within the deep white matter The tumor presents a combination of solid,cystic and calcified components. (C). Post-contrast axial T1-w image (D) shows no pathological enhancement and axial CT scan (E) confirms the calcified component. Coronal IR T1-w image (F) demonstrates lesion resection; G: Histological examination evidences a biphasic neoplastic population, with neuronal and glial elements.

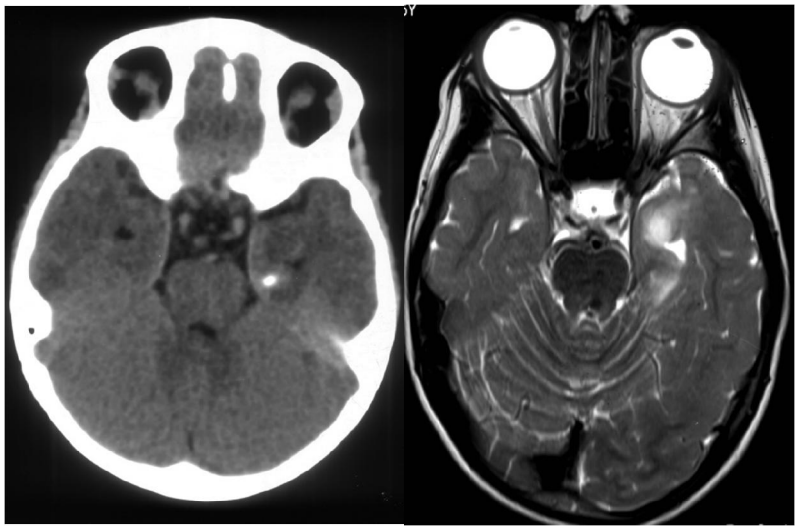

Fig 5:Ganglioglioma of medial temporal lobe showing calcification in axial CT brain with combination of solid cystic cortical subcortical mass in T2 MRI

Dysembryoplastic Neuroepithelial Tumors (DNETs)

Dysembryoplastic neuroepithelial tumors (DNETs) are always WHO grade I intra axial neoplasms that were first described by Daumas-Duport in 1988[25]. They are composed of oligo- dendrocyte like cells that are attached to bundles of axons while neurons float in a myxoid interstitial fluid. These columns of the so-called glioneuronal element are oriented perpendicularly to the cortical surface. On MRI, a DNT appears as usually multilobulated cysts, rarely only one large cyst is present. The cysts represent the glioneuronal element and are located in the cortex or in the cortex and subcortical white matter, sometimes single smaller cysts are located in the vicinity of the tumor, from which they are clearly separated. The multilobulated cysts are characteristically hypointense on T1-weighted and strongly hyperintense on T2-weighted images. On FLAIR images, they have mixed signal intensity, most of the "lobuli within the cyst" are

hypointense(figure 5[26]). On DWI, DNTs are hypointense. Parts of the glioneuronal element may show contrast enhancement, calcifications are rarely found

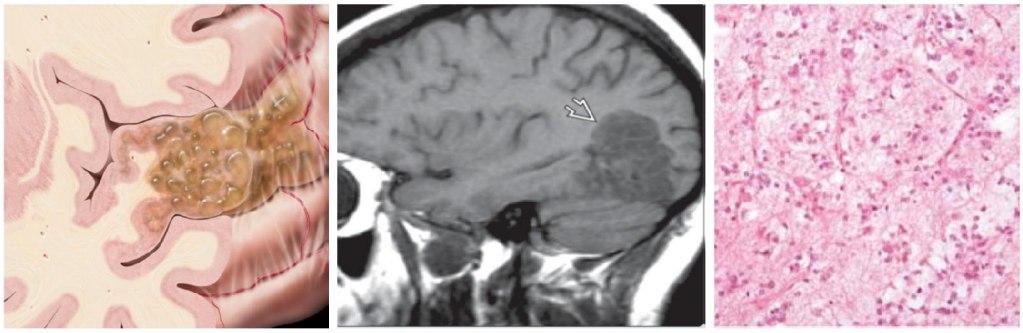

Figure 6:Coronal oblique graphic shows the typical appearance of a cystic cortical DNET. The gyrus is expanded by the multicystic-appearing tumor Sagittal T1 MR image in a young adult with seizures shows the characteristic "bubbly"appearance of a DNET. Note the low T1 signal within the wedge-shaped cortical mass Microscopic study evidences the presence of floating neurons, a feature of DNET, in microcystic areas lined with oligo-like cells

Angiocentric Neuroepithelial Tumors (ANETs)

This entity was recently described by two different groups from Paris, France and Houston, USA in together 18 patients almost always suffering from epileptic seizures since childhood.[27] Histologically, the variably infiltrative tumors had features of both astrocytoma and ependymoma, the most striking neuropathological features were an angiocentric polarity with gliofibrillary acidic protein (GFAP) positive fusiform and bipolar astrocytic cells arranged around blood vessels.

On MRI these tumors were located in the cortex and subcortical white matter with a stalk like extension to the lateral ventricle. On T1-weighted SE sequences, the involved cortical gyri were isointense with an intrinsic

rim like hyperintensity.On T2-weighted and FLAIR sequences the tumors were hyperintense. There were no calcifications or contrast enhancement (figure 7[26]).

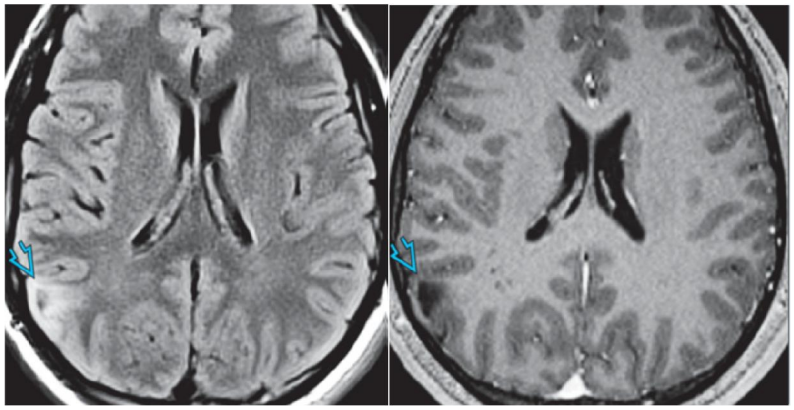

Figure 7:Axial FLAIR MR shows a wedge shaped hyperintense cortical and subcortical mass in the right parietal lobe,lack of surrounding edema. Axial T1 C+ MR in the same patient shows no enhancement within the mass, a typical finding in angiocentric glioma.

Glial Tumors

Pilocytic Astrocytomas :

Pilocytic astrocytomas are generally circumscribed, slowly growing, often cystic astrocytomas, histologically characterized by a biphasic pattern with varying proportion of compacted bipolar cells with Rosenthal fibres and loose textured multipolar cells with microcysts and granular bodies. They correspond to WHO grade I tumors although rarely anaplastic pilocytic astrocytomas are found. On MRI, pilocytic astrocytomas are well-circumscribed mass lesions with a cystic portion and a contrast-enhancing mural nodule(figure 8[4]). It may be impossible to distinguish this tumor from a ganglioglioma, calcifications, e.g., which are present in one third of gangliogliomas, would favour the diagnosis ganglioglioma. In rare cases, a

pilocytic astrocytoma spreads through the subarachnoid space, although histologically it may be still a WHO grade I tumor.

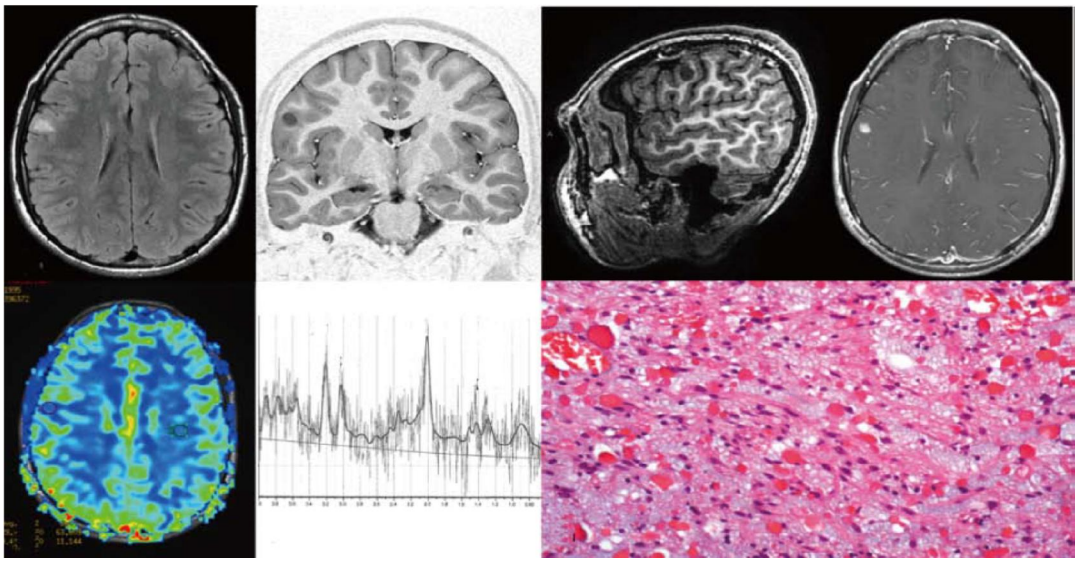

Figure 8:Pilocytic astrocytoma World Health Organization grade I of the right frontal lobe. Axial FLAIR T2-w (A) and coronal lR T1-w (B) images show a cortical-subcortical lesion, with cystic component, with minimal mass effect. The tumor appears well demarcated (C) on 3D sagittal sequence and displays nodular and homogeneous enhancement on post-contrast axial T1-w images (D). Perfusion study doesn't show any rCBV increase within the lesion (E). MR Spectroscopy (MRS) study (F) reveals elevation in choline and reduction in NAA. (G) Histological examination shows a tumor composed of areas rich in myxoid material, elongated glial elements with uniform nuclei and numerous eosinophilic granular bodies

Diffuse Astrocytomas

Diffuse astrocytomas are diffusely infiltrating primary brain neoplasms of astrocytic origin that are classified as WHO grade II.Diffuse astrocytomas are usually at unenhanced CT iso to hypoattenuating lesions. They do not enhance on post-contrast imaging. Calcifications may be present in approximately 20%; cyst formation is rare.

MRI demonstrates astrocytomas as relatively homogenous mass involving and expanding more typically cerebral hemispheres cortex and adjacent white matter. The lesions are high in water content, thus appearing as

hyperintense on T2 weighted images and hypo isointense on T1 weighted sequences. They usually lack peritumoral oedema. Well differentiated Astrocytomas has a variable appearance after contrast agent administration, but usually shows no significant contrast enhancement.In general, contrast enhancement is not recognized as a reliable indicator of the grade of infiltrative astrocytomas. MR perfusion imaging however seems to be more informative for distinguish low- and high-grade astrocytoma and for identifying low-grade lesions that could more likely behave aggressively[27].On dynamic contrast enhanced T2 weighted MR perfusion imaging study rCBV is typically less than 1.75[28]. MR Spectroscopy should display Cho elevation and NAA reduction. A High myo-inositol to Creatine ratio (Myo/Cre) in also present

Pleomorphic Xantoastrocytomas

Pleomorphic xanthoastrocytomas (PXAs) are astrocytic tumors with superficial location in the cerebral hemispheres and involvement of the meninges. They correspond histologically to WHO grade II, for lesions with significant mitotic activity (five or more mitoses per ten high-power fields) the term PXA with anaplastic features may be used. It has been postulated that PXAs originate from subpial astrocytes. However, the demonstration of synaptophysin and neurofilament protein in some PXAs can be taken as evidence for neuronal differentiation and suggests a more complex histogenesis. On MRI, PXAs have typical imaging features with a

meningio-cerebral contrast enhancement on T1-weighted and white matter edema on T2-weighted and FLAIR images. Calcifications are possible and as a glial tumor, a PXA usually has a space-occupying effect(figure 9[26]).

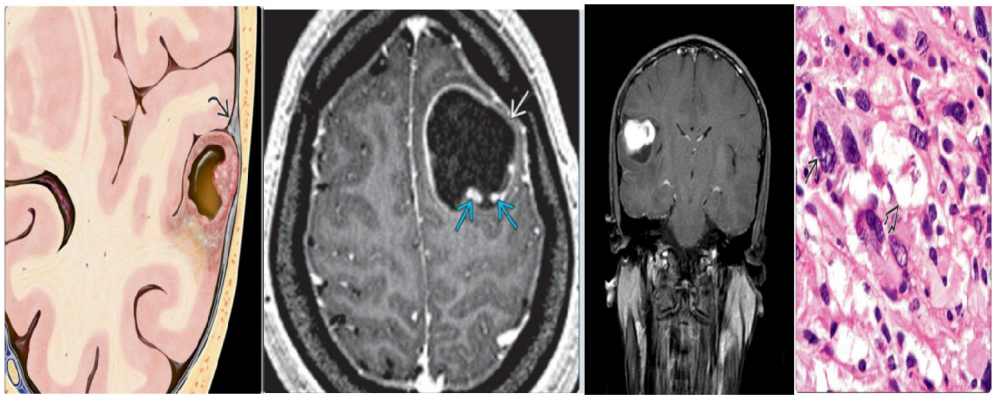

Figure 9:Coronal graphic shows a cystic and solid cortical mass with thickening of the adjacent meninges Axial T1 C+ MR image shows a peripherally located frontal lobe mass, which abuts the dura with mild local mass effect. Solid, enhancing mural nodules are present Conspicuous pleomorphism of the tumor with multinucleated giant cells and vacuolation characteristic for PXA, WHO grade II.

FOCAL CORTICAL DYSPLASIA AND LEAT

LEAT and focal cortical dysplasia FCD are common findings in drug-resistant focal epilepsies, and frequently coexist[29 30].

Rarely MRI features of LEAT could be misinterpreted as FCD. Generally most important neuroradiological findings in FCD are increased cortical thickness, blurring of the cortical-white matter junction, increased signal on T2W, a radially oriented linear or conical transmantle stripe of T2 hyperintensity, cortical thinning, and localized brain atrophy[31].

Some limitations are encountered in the correct identification of different FCD types or subtypes[32]. A high number of false negatives is detected with

FCD type I and slightly fewer with FCD type IIa (about 50% sensitivity). FCD IIb is much more easily identified (about 90% sensitivity)[33]

Molecular genetics and pathogenesis

In May 2016, the revised WHO classification of tumours of the central nervous system was released[34] and has already revolutionized the arena of neurooncology. It is for the first time in the blue book series of brain tumours that molecular genetic information is required for an integrated phenotypic genotypic diagnosis[35], and this applies to diffusely infiltrating glial and embryonal tumours.

However, this successful multidisciplinary strategy has not been developed norMsystematically applied for LEAT, and tumour entities lacking ample evidence for distinct molecular-genetic signatures have fallen behind this rapidly developing process.

As histopathological classification systems will be continuously updated and revised, the WHO's current roadmap towards better understanding of carcinogenesis and personalized treatment needs to be adopted to LEAT. It is now generally accepted and also recognized in the 2016 WHO classification, that LEATs lack IDH1 or IDH2 mutations as well as 1p/19q codeletions[36] Published literature on prevalent molecular alterations in LEAT point to the RAS/RAF/MAPK pathway and the PI3K/AKT/mTOR pathway (Figure 10). BRAF V600E mutations were most consistently

reported as genetic driver in gangliogliomas (18-56%). It's variable detection also in DNT (0-50%)40-48 may reflect, however, the aforementioned difficulties in separating both tumour entities at the microscopic level [37]As BRAF V600E mutations were observed also in pleomorphic xanthoastrocytomas [38] and pilocytic astrocytomas[38] their presence cannot be regarded yet as specific for a given tumour entity. In DNET, tyrosine kinase activating *FGFR1* gene mutations prevail (58-82%)[38]whereas *MYB/MYBL1* alterations were encountered in 87% of angiocentric gliomas[37], another LEAT tumour entity associated with drug-resistant epilepsy and early seizure onset. A methylation-based classification from visually selected tumour regions of formalin fixed and paraffin embedded tissue represents a promising new option[39], but has not been systematically applied and validated for the entire LEAT spectrum. Use of mutation specific antibodies, i.e. directed against the V600E BRAF mutation[40], may help to further explore the extent of cellular and genetic mosaicism . It needs to be shown, however, if such features also contribute to the epileptogenic phenotype. These studies need a careful design based on a validated histopathological classification scheme.

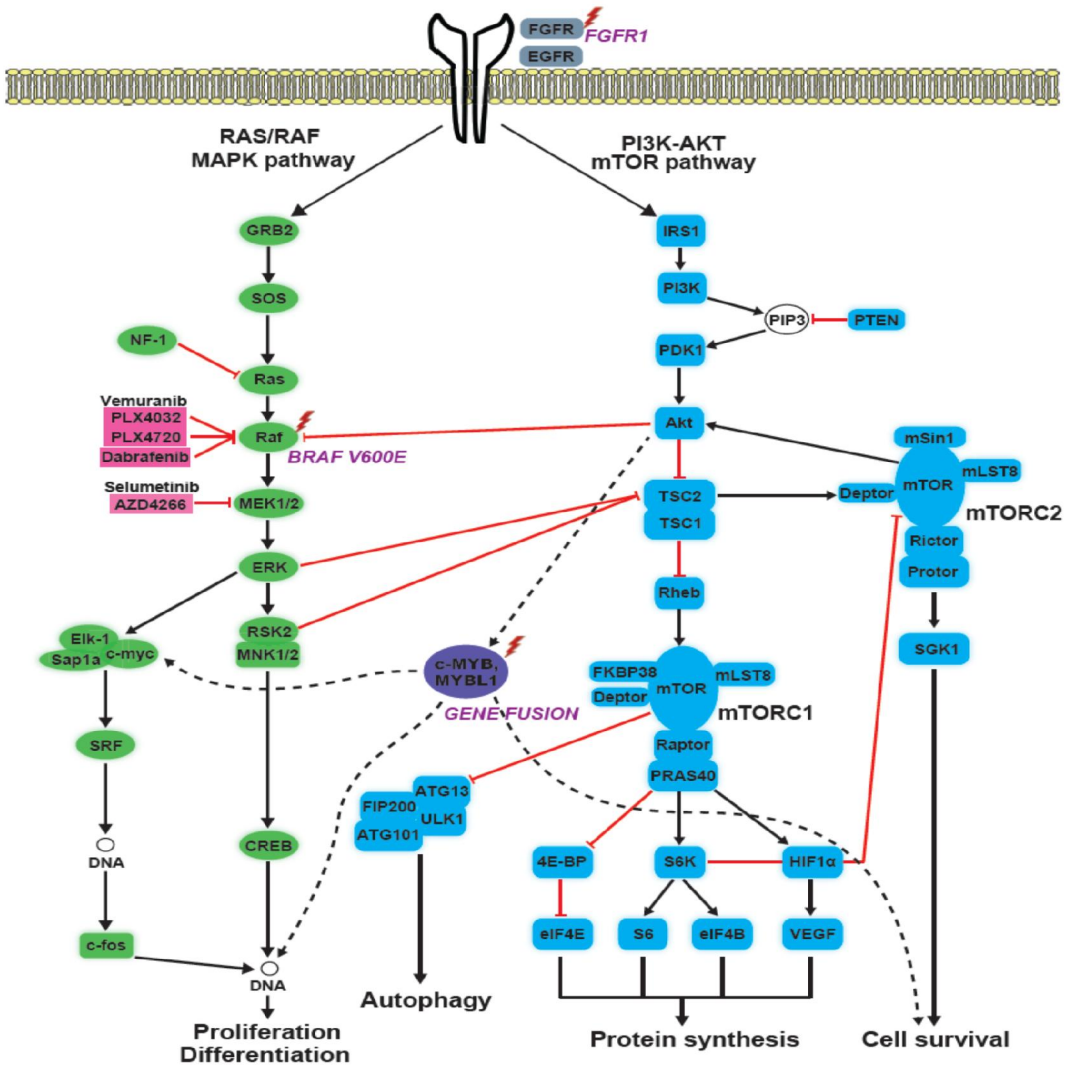

Figure 10:Genetic alterations commonly found in LEAT connect 2 major pathways in cell metabolism, the RAS/RAF/MAPK pathway (green) and the PI3K/AKT/mTOR pathway (blue). Upstream in receptor signalling, mutations of FGFR1 have been described in DNET leading to activation of the RAS/RAF/MAPK pathway and the PI3K/AKT/mTOR pathway.

BRAF is a component further downstream in the RAS/RAF/MAPK signalling cascade. Activation of this pathway by the V600E mutation leads

to phosphrylation of MAPKs, which phosphorylate and regulate activities of partners such as transcriptions factors (CREB, c-fos) for cell proliferation and differentation. These functions made BRAF and MEK1/2 reasonable targets for therapeutic approaches (pink). On the other hand activation is tightly regulated by substrates of the PI3K/AKT/mTOR signalling cascade. Especially, the inhibiting function of the 2 major complexes TSC and mTOR play a profound role in the regulation of autophagy, protein synthesis and cell survival. One of these transcription factors is c-myb/ mybl1(purple) which is altered in angiocentric gliomas.

Mechanisms of epileptogenesis

Two major hypotheses underly the pathogenic mechanism of focal hyperexcitability causing epilepsy in patients with a LEAT [41]. The first hypothesis is that the neuronal component of the tumour is functionally integrated into excitatory circuitries[22].Using immunohistochemistry and electrocorticography (ECoG), Ferrier *et al.* reported that the high neuronal density in the lesion of GNT is associated with epileptiform discharge patterns and that the expression of specific glutamate receptor (GluR) subtypes (ionotropic and the metabotropic glutamate receptors (iGluR and mGluR)) in the neuronal component of GNT are highly upregulated [41].

More recent studies analysing the gene expression profile of GG in a single cell analysis, revealed the prominent expression of the mGluR5 in the dysplastic neuron components, supporting the existence of developmental

alterations in the balance between excitation and inhibition within the lesion[42]. Glutamate appears to play an important role in the biology of glial tumours and their epileptogenicity [43]. In neurons, glutamate is released exclusively through synaptic vesicles and requires a Ca2+ dependent fusion event, whereas in glial cells, glutamate is released in several ways including vesicular release, reverse operation of the Na+ dependent glutamate transporters, swelling activated anion channels or through hemichannels[44]. In gliomas, glutamate release has been shown to occur the system xc- cysteine glutamate transporter [44]. It is Na+ independent, transports cysteine into the cell in return for glutamate being released, triggers electrical activity in gliomas cell lines [44] and thus contributes to neuronal hyperexcitability and epileptic activity[45]. Moreover a low level of glutamate receptor GluR2 is also associated with increased alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor Ca2+ permeability in gliomas, which is proposed to be the epileptogenic mechanism in these tumour types [41]. In both glial and glioneuronal tumours, a lower level of expression of glial glutamate transporters has been observed thereby increasing the extracellular glutamate concentration contributing to tumour epileptogenesis . Remarkably, mGluR5 which is expressed in both gliomas cells in vivo and in vitro is known to down regulate the expression of glial glutamate transporters in vitro[46] . Altered expression of gap-junction channels (connexins), such as overexpression of connexins 32, leads to

disturbed communication between cells which possibly contributes to epileptogenesis in GNTs [47]. Disturbance of potassium homeostasis caused by, both, reduced inwardly rectifying K+ channel currents and mislocalization of Kir4.1channels has also been reported as a potential mechanism underlying tumour associated epilepsy[41]. The increasing evidence of the involvement of pro-inflammatory molecules in GNTs leads to hypothesis that the prominent increased expression of the immune response coupled with the activation of the complement cascade along with the production of pro-inflammatory cytokines observed in brain tumours, induces alteration of the blood brain barrier (BBB) which leads to tumour epileptogenicity[41]. Modification of the components of the Pi3K-mTOR signalling pathway has shown that this pathway has a critical role in epileptogenesis of GNTs[42].

The second hypothesis involves the changes in the tumour-associated epileptogenic adjacent brain (peritumoral region), which has been shown to be an important aspect[48]Resecting only the lesion does not achieve complete seizure relief in patients, supporting the idea of the role of the peritumoral region in epilepsy [49]. Phenomena such as disturbed morphology, neuronal migration, changes in synaptic vesicles, persistent neurons in white matter, imbalances between inhibitory and excitatory mechanisms through changes in GABA and glutamate homeostasis, hypoxia, acidosis and enhanced

intercellular communication through increased expression of gap junction channels in the peritumoral region have been suggested to contribute to epileptogenesis[6].

Recently, few studies have shown that changes in the peritumoral region of neuronal expression of NKCC1 leads to a positive shift of EGABA (inducing a depolarized reversal potential); and enzymatic changes such as dysregulation of adenosine kinase (ADK)leading to neuronal excitability [50].

To conclude, the potential contribution of peritumoral cortical disorganisation in coexistence with cortical dysplasia has to be considered strongly in GNTs [41].

Indeed the identification of a coexistent pathology may be clinically relevant since it has been extensively reported that the tumor itself may be electrically silent and the origin of seizures is from a pathological tissue adjacent to the tumor[51]. The implication is that excising the tumor and leaving in place the nearby abnormal epileptogenic tissue, may give unsatisfactory results on the seizure outcome. Young age and long duration of illness are associated with an increased risk of secondary epileptogenesis. GNT can be intrinsically epileptogenic,even when associated with FCD[52].

Secondary epileptogenesis

For about a third of patients, the epileptogenic focus does not correspond to tumour location. Such secondary epileptogenesis implies that an actively discharging epileptogenic focus induces similar paroxysmal activity in regions that are distant to the original site. This secondary focus is seen more frequently with temporal tumours.[53]Young age and long duration of illness are associated with an increased risk of secondary epileptogenesis. Therefore, early treatment of the primary epileptic lesion may be needed to prevent development of a secondary, potentially irreversible, focus.[54]

Epileptogenesis in patients with brain tumours is probably multifactorial and caused by different tumour types and changes in the properties of tumour-cell membranes that generate action potentials and thus affect neuronal excitability (eg, raised concentrations of aminoacids, neuroreceptor disturbances, increased gap junctions between tumour cells, and low pH microenvironment)

CLINICAL AND EEG FEATURES OF FOCAL EPILEPSY ASSOCIATED WITH LEATs

Clinical features

Focal epilepsy is the most common and often the only symptom of LEAT. Neurological deficits are relatively uncommon, varying from 0% to 15% according to different series: the neurological sparing might depend on the indolent and slow course of LEAT that might allow compensation of

possible brain impairment by slowly developing plastic processes, particularly in the young age. Epilepsy can appear at any age: however, the majority of cases present with an epilepsy onset in adolescence and young adulthood. In DNET, seizures appear almost always and more than half of the patients have focal seizures with alterated consciousness, with or without secondary generalization[55]. Regarding GGs, 80%-90% of patients seizures represent the only clinical symptom (mainly secondarily generalized tonic-clonic seizures)[56].

Seizure semiology is related to the site of tumor. In general, complex partial seizures with aura are more common in LEAT located in the temporal lobe, whereas secondary generalization is more common in epilepsies associated with extratemporal LEAT[57]. However, the extension of the tumor-related epileptogenic area may vary according to the anatomical location of the neoplasm: in fact, several data suggest that epileptogenic zone may be more widespread and complex in focal epilepsies associated to LEAT in the mesial temporal lobe in comparison to neocortical temporal lateral locations . Occurrence of status epilepticus has been reported to be rare.

Clinical parameters that differentiated patients operated on in childhood from patients operated on in adulthood were: (1) aura that was reported more often in the adult group, but it should be noted that this finding might at least partially depend on the fact that, in general, children are less able to

refer their auras; and (2) mean age at seizure: probably due to the fact that developing brain has a low seizure threshold which leads to early and frequent seizures. Moreover, in pediatric age, malformations of cortical development are most often the basis of lesional epilepsy that is characterized by a high seizure frequency that can facilitate an early diagnosis and that can lead to early evaluation for a surgical approach. No differences between the clinical features of epilepsy associated with DNET and with GG have been reported [42,89]. A favourable seizure outcome has been observed in cases with a short duration of epilepsy, only partial seizure and the lack of secondary generalization .

EEG features

Usually interictal EEG shows spikes and/or, sharp waves, sometimes intermixed with slow activities; in some instances normal EEG have been reported. These abnormalities, in preoperative EEG are commonly lateralized to the tumor side, less often to the correct lobe. However, Morris *et al* (1998) reported that the occurrence of interictal EEG abnormalities and ictal EEG onset in correspondence of the site of the tumor may not be predictive of seizure outcome; indeed, in some cases a postoperative poor seizure outcome has been reported in patients with EEG interictal and ictal findings perfectly concordant with tumor location. On the other hand, also patients with EEG slow or epileptiform abnormalities distant from the tumor

site or with ictal EEG onset nonlocalized or widespread to a whole hemisphere improved regarding seizure outcome after tumor resection[57]. In temporal lobe LEAT, long-term video-EEG monitoring may allow recording of seizures and identification of the epileptogenic zone; indeed, several data suggest that in mesial temporal lobe LEAT a tailored resection that include, besides the tumor, the epileptogenic area as defined by the anatomic and electroclinical correlations performed on the ictal video-EEG data, provides better post-operative seizure outcome as compared to simple lesionectomy[58]. In cases of undetermined lateralization of seizure focus, invasive EEG investigations may provide useful information, although in LEAT associated focal epilepsy the main goal of intracerebral recordings is usually to map eloquent cortex in proximity of the neoplasm. Several reports focused on prediction of poor postoperative outcome by identifying ECoG spike discharge patterns in FCD and the persistence of seizure patterns or continuous epileptiform discharges in post-resection ECoG recordings . There are little evidences about the ECoG discharge patterns in patients with LEATs because of the small numbers of patients investigated[59] [60]. Different disorders (LEAT and FCD) may have similar electrocorticographic abnormalities probably due to the common developmental origin. In these cases have been observed continuous spiking (more often in FCD), bursts, and recruiting discharges. When continuous

spiking is found in LEAT, it is likely to be due to associated dysplastic regions with a high neuronal density[60]

SURGICAL STRATEGIES FOR LEAT

Epilepsies associated to LEAT are usually unsatisfactorily controlled by antiepileptic drugs, whereas excellent results can be achieved by surgery[61 1]. Various surgical approaches have been adopted for the radical resection of these tumors. The choice of surgical approach is also related to the goal of surgical strategy.

The surgical strategy may be directed only to oncological issues and/or to resolve epilepsy. In this last condition we must have an epilepsy surgery oriented approach. A non-invasive presurgical study and neuropsycological assessment**,** may define the extension of the epileptogenic zone and may address the choice of the better surgical strategy to optimise seizure control (lesionectomy or tailored resection)[62]. Rarely in the setting of epilepsy associated tumor may be necessary an invasive presurgical study (using subdural grid, depth electrodes, or stereo-EEG[63]

LEAT are certainly the prototype of cases where epilepsy is the main problem. However, in recent years, even in cases where the main problem is oncological, it is becoming equally important trying to preserve brain functions and to best cure even epilepsy (especially when tumors involve

mesiotemporal structures, the insular lobe, or the central area) in order to improve the quality of life[7]

Several authors analyzed epileptological outcome according to surgical treatment in tumor-related chronic epilepsy. While some argue that lesionectomy alone is enough for good seizure control others say that the best management should include additional resection of epileptogenic zones adjacent to the tumor[64]

In Epilepsy-associated tumors it reaches a special meaning for the epileptogenicity and surgical strategies, the site of the lesion, *i.e.*, temporal, mesio-temporal (or limbic), temporo-lateral, paralimbic, extratemporal, eloquent areas[8 64 58 65]. Regarding limbic and paralimbic system, the role of hippocampus in the epilepsy network is pivotal since that could play a pivotal role in epileptogenesis even without obvious neuroradiological and pathological changes (*i.e.*, hippocampal sclerosis)[8 64 58 65].

The limbic system consists of the following elements, which are all directly or indirectly interconnected: the temporo-mesial structures (hippocampus, the parahippocampus gyrus) and the cingulate gyrus[66 65 67]. The paralimbic system is composed of 3 independent anatomical parts: the orbitofrontal cortex, the temporopolar cortex, and the insula[66 67]The limbic system is connected *via* the entorhinal cortex and the uncinate fasciculus to the

paralimbic system. In the setting of low grade tumors associated with epilepsy WHO Grade gliomas are mainly found in the paralimbic system while glioneuronal tumors are found in the limbic system (temporomesial structures)[68]

LEAT are frequently associated with type or type a cortical dysplasia which, in contrast to focal cortical dysplasia type b, are more difficult to identify with MRI. It means that the anatomical structural lesion can be larger than what have been detected by MRI[69].For this reason the target of the surgical resection should be the epileptogenic zone defined according to neuroradiological, clinical, neurophysiological and neuropsycological findings[70].

In case of LEAT located near or in eloquent area, the surgical approach is usually directed only to the anatomical structural lesion. Regarding the more frequent site of these tumors, *i.e.*, the temporal lobe, several approach have been used. The surgical strategy used in temporal lobe tumors includes lesionectomy, extended lesionectomy, tailored resection, anterior temporal lobectomy.

The majority of authors agree that lesionectomy alone provides the best seizure outcome results in LEAT located in the extratemporal and temporo-lateral site[71]while its results for temporomesial lesions are questionable[1 8].

Some authors suggested that the involvement of temporo-mesial regions may extend and make more complex the epileptogenic zone. For this reason the amount of tissue removed in temporomesial surgeries is considered crucial to gain good postoperative results[1 8 65]. One important and persistent problem are the conflicting needs of the necessary extent of resection and the avoidance of neuropsychological deficits

Epilepsy Surgery Outcome Scales

The appropriate evaluation of patients following epilepsy surgery is extremely important, as medical professionals must know the appropriate course of action to follow in order to achieve seizure freedom for patients[60] Accordingly, the Engel classification guidelines were devised by UCLA neurologist Jerome Engel Jr. in 1987 and made public at the 1992 Palm Desert Conference on Epilepsy Surgery. The Engel classification system has since become the standard in reporting postoperative outcomes of epilepsy surgery.

Engel Outcome Scale

Class I: Free of disabling seizures

- IA: Completely seizure-free since surgery
- IB: Non disabling simple partial seizures only since surgery

- IC: Some disabling seizures after surgery, but free of disabline seizures for at least 2 years
- ID: Generalized convulsions with antiepileptic drug withdrawal only

Class II: Rare disabling seizures ("almost seizure-free")

- IIA: Initially free of disabling 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

- IIIA: Worthwhile seizure reduction
- IIIB: Prolonged seizure-free intervals amounting to greater than half the follow-up period, but not less than 2 years

- Class IV: No worthwhile improvement
    - IVA: Significant seizure reduction
    - IVB: No appreciable change
    - IVC: Seizures worse

ILAE Outcome Scale

In 2001, the International League Against Epilepsy (ILAE) proposed a new classification scheme for outcome with respect to epileptic seizures after surgery. The goal of this classification scheme was to provide a more objective measure of the number of seizures

- Class 1: Completely seizure free; no auras
- Class 2: Only auras; no other seizures
- Class 3: 1 to 3 seizure days per year; ± auras
- Class 4: 4 seizure days per year to 50% reduction of baseline seizure days; ± auras
- Class 5: Less than 50% reduction of baseline seizure days; ± auras
- Class 6: More than 100% increase of baseline seizure days; ± auras

MATERIAL AND METHODS

MATERIAL AND METHODS

Retrospective study of consecutive patients who underwent surgery for epilepsy for Long Term Epilepsy associated tumors (LEAT) from 1998 to 2016 and having a minimum one year of follow up . Their clinical features, EEG,imaging data,operative findings, post operative hospital course and condition at discharge was recorded from the SCTIMST epilepsy surgery database. Follow up at 6 months, 1 year ,1.5 year and last available follow up was noted from the out patient records.

Inclusion criteria:

- Patients who were operated for lesional epilepsy and histology suggests Long Term Epilepsy associated tumors (LEAT) like DNET, ganglioglioma (from 1998 to 2016) and who underwent a pre surgical work up for drug resistant epilepsy.

Exclusion criteria:

- Presence of other tumor on histopathology like high grade astrocytoma or glioblastoma
- Patient without electrophysiological concordance
- Patients operated as emergency without pre operative evaluation

Preoperative MRI films was reviewed to delineate the site, size, extent of tumor, contrast enhancement, calcification, cystic changes, mass effect, and

associated hippocampal atrophy or sclerosis (MTS/HS) and dysplastic changes. Collateral sulcus was used as the boundary between the medial and lateral location of the tumor in the temporal lobe. In extra temporal location, the tumors were noted to be either confined to one of the lobes (frontal, parietal or occipital) or multilobar when it extended beyond one lobe. A post-operative MRI was done for all patients after surgery at various periods of follow-up.

All surgeries were undertaken under general anesthesia. When the lesion is confined to the limits of the collateral sulcus i.e. in the mesial temporal lobe, a lesionectomy encompassing amygdalohippocampectomy was undertaken. If lesion extended into mesial and lateral temporal region, a standard anterior temporal lobectomy with amygdalo hippocampectomy (ATL) was performed with5–5.5 cm and 6–7 cm of lateral neocortical resection respectively on left and right sides. If the lesion was confined to the temporal neo-cortex or extra temporal locations in a single lobe, a lesionectomy alone was performed. “completeness of resection” was defined as complete removal of lesion as noted in post-operative MRI.

Pathological examination

Four-micrometer-thick histologic sections were generated from10% formalin fixed, paraffin-embedded tissue and stained with hematoxylin and eosin (H&E). 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), Neu N, chromo-granin (Novacastra, Newcastle upon Tyne,UK;1:100 dilution) etc were used regularly as and when indicated

Outcome assessment

The following variables were assessed according to their importance in presurgical evaluation of refractory epilepsy-age at surgery, age at onset of habitual seizures, duration of epilepsy prior to surgery, history of initial precipitating injury (febrile seizures, meningoencephalitis or status epilepticus), secondary generalized seizures, concordant interictal epileptiform discharges (IEDs, >75% on the side of MRI abnormality/ resected lobe), grade of excision which was classified into 2 categories for data purposes: gross total and subtotal which includes neartotal and subtotal, pathology, and presence of spikes in post-operative EEGs. Patients were regularly followed up at 3,6,12 and 18 months after surgery and at yearly intervals thereafter.

Seizure outcome was assessed according to the Engel's scale. Seizure control was classified into 2 groups: favorable (Engels Class I and II) or unfavorable (Classes III and IV). Post-operative seizure outcome was categorized as "excellent" if the patient remained seizure-free at all times of

follow-up with or without antiepileptic drugs (AEDs), ”good outcome” if they have gone into remission with or without AEDs in the last 2 years of follow-up (“favorable outcome”) and the rest as “unfavorable outcome”.

Statistical methods :

Quantitative data are summarized as mean ± standard deviation (SD). Categorical data are summarized as proportions and 95% confidence intervals. Pearson’s Chi-square test, Fisher’s exact test and Student’s t-test were used to evaluate the statistical significance of the association of different clinical, EEG, MRI and histological characteristics with the seizure outcome at last follow-up. Continuous variables were analyzed by t test and categorical variables by Chi square test or Fisher’s exact test. The level of statistical significance was set at p value < 0.05. Univariate logistic regression analysis was used to assess the prognostic importance of each of the above variables. The factors which attained significance in the univariate analysis were carried on to multivariate Cox proportional hazards regression model. Hazard ratios were used to express the strength of association. Wald statistics re-confirmed the statistical significance. Kaplan–Meier survival analysis was used to calculate the probability of seizure freedom with time. All statistical analysis were done using the SPSS Statistics software version 17.0 (SPSS Inc., Chicago, IL, U.S.A).

RESULTS

Results

This is a Retrospective study of patients who underwent surgery for epilepsy for Long Term Epilepsy associated tumors (LEAT) from 1998 to 2016 and having a minimum one year of follow up

198 patients underwent surgery during this period and 19 patient was excluded due to non availability follow up and preop data

Patients characteristics

Off the 179 patients included in this study the mean age was 19.4+12.o and age ranges from 1 to 63 years ,median age is 17 years with interquartile range 11-25 years.(table 3) Median age at epilepsy onset was 10 years(IQR-4-16 years) median duration of symptoms was 72 months(IQR-24-132 months).(table 3)

	N	Mean	sd	Minimum	Maximum	Median	25th percentile	75th percentile
Age	179	19.4	12.0	1.0	63.0	17.0	11.0	25.0
age_at_onset_of_symptoms	179	12.1	11.4	0.3	62.0	10.0	4.0	16.0
duration_of_symptoms	179	88.7	82.0	0.3	516.0	72.0	24.0	132.0

Table 3

In this study 108(60.3%)were male and 71(39.7%)were females(table 4 and fig 11)

Gender	Frequency	Percent
Male	108	60.3
Female	71	39.7
Total	179	100.0

Table 4

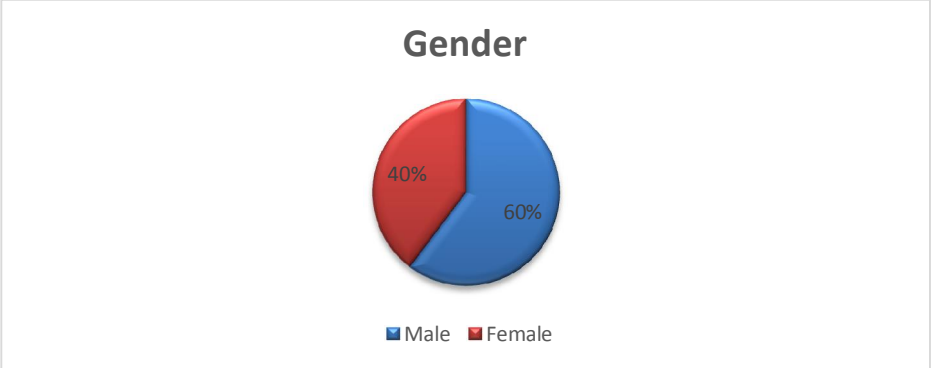

Fig 11:gender distributions

Febrile seizures noted in 16(8.9%)patients(table 5)

Febrile seizures	Frequency	Percent
Yes	16	8.9
No	163	91.1
Total	179	100.0

Table 5

Aura noted in 105(58.7%) patients (table 6)

Presence of aura	Frequency	Percent
Yes	105	58.7
No	74	41.3
Total	179	100.0

Table 6

166(92.7%) patients presenting symptoms was seizures alone and 11 patients (6.1%) presented with focal deficit in form of mild hemiparesis and 3 patients(1.7%)with visual field deficit and 3 patient(1.7%) with symptoms of raised ICP and 19 patients(9.5%) with mild headache along with seizures(table 7 and fig 12)

Symptoms	Frequency	Percent
Seizures	166	92.7
FND	11	6.1
Raised ICP	3	1.7
Head ache	19	10.6
Field defects	3	1.7

Table 7

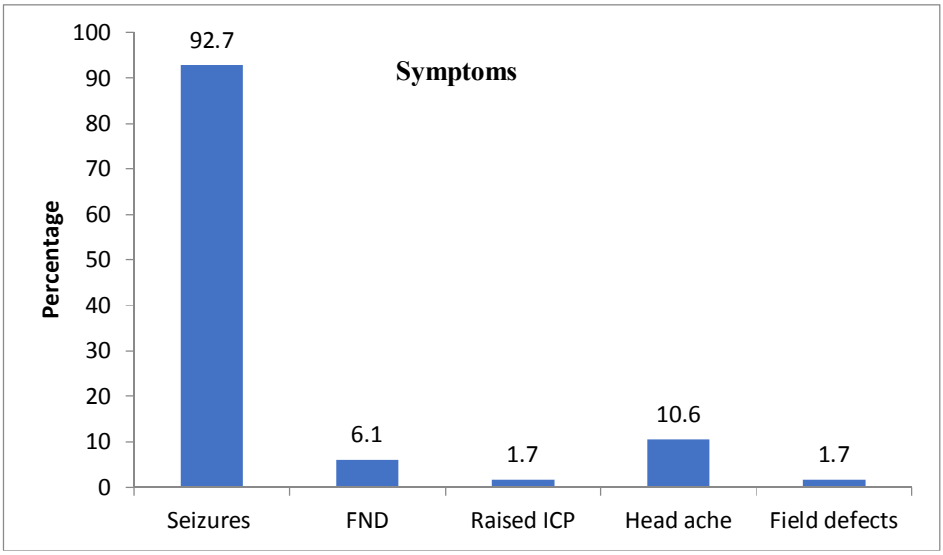

Fig:12 symptomatology

In this study majority of patient had seizures frequence more than 5 per month(table 8)

Seizures_frequency	Frequency	Percent
1-3	51	28.5
4-5	49	27.4
>5	79	44.1
Total	179	100.0

Table 8

Complex Partial Seizures occurred in majority 95(53.1%) and CPS with secondary generalization in 38% and GTCS in 8.9%(table 9 and fig :13)

Type of Seizure	Frequency	Percent
Focal	95	53.1
Focal with Generalization	68	38.0
GTCS	16	8.9
Total	179	100.0

Table 9

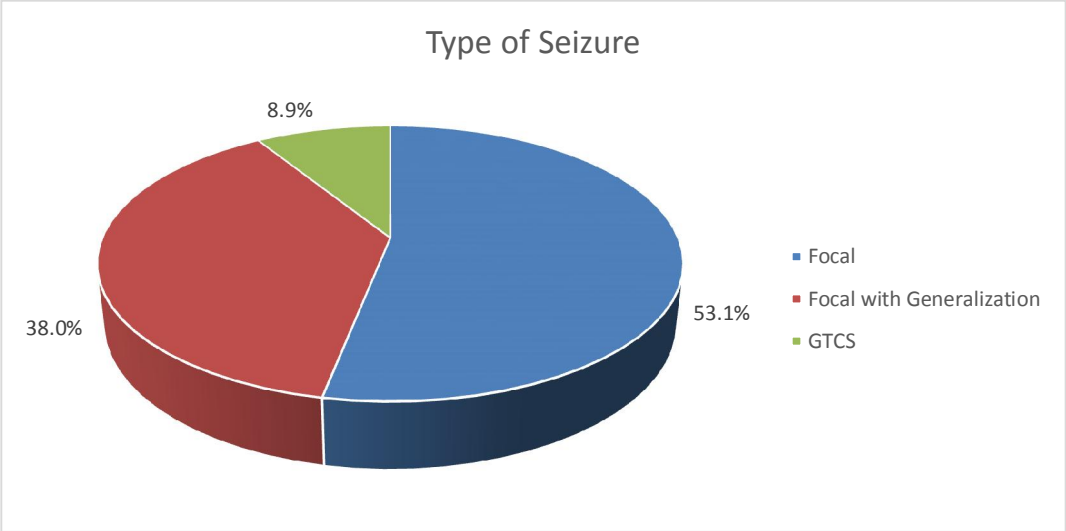

Fig 13:seizure types

Neuroimaging findings:

There were 102 temporal tumors 11 in mesial location, Of 77 with extra temporal tumors, there were 29 with frontal lesions, 18 parietal, 7 occipital, 2 hypothalamic, 8 insular and 2 chiasmal(figure 14)

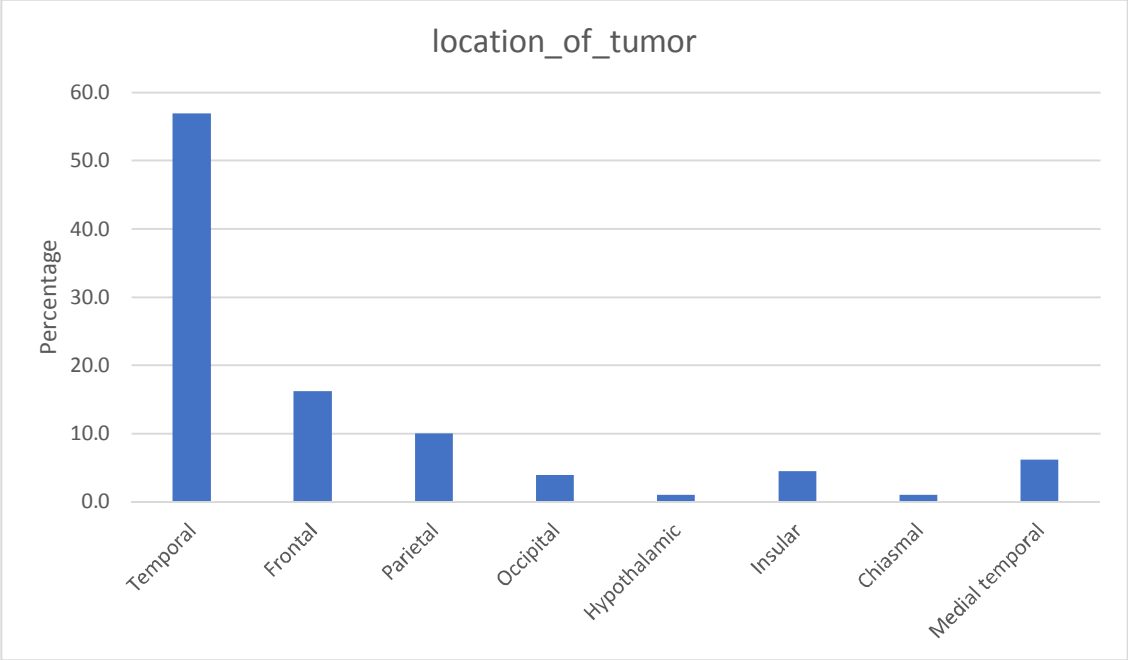

Fig 14:location of tumors in the study

In 179 patients 90(50.3%) patients had lesion on left side and 89 patients (49.7%) was on right(table 10) .In majority(54.2%)of patient tumor size was between 3-5cm(table 11) and 53.6% lesion was contrast enhancing in imaging (table 12)and calcification was present in 31.8%(table 13)

Side	Frequency	Percent
Right	89	49.7
Left	90	50.3
Total	179	100.0

Table 10

size	Frequency	Percent
<3cm	63	35.2
3-5 cm	97	54.2
>5cm	19	10.6
Total	179	100.0

Table 11

Contrast enhancement	Frequency	Percent
Yes	96	53.6
No	83	46.4
Total	179	100.0

Table 12

Calcification	Frequency	Percent
Yes	57	31.8
No	122	68.2
Total	179	100.0

Table 13

29 patients(16.2%) patient had associated MTS/HS(table 14,fig 15)

Associated MTS/HS	Frequency	Percent
Yes	29	16.2
No	150	83.8
Total	179	100.0

Table 14

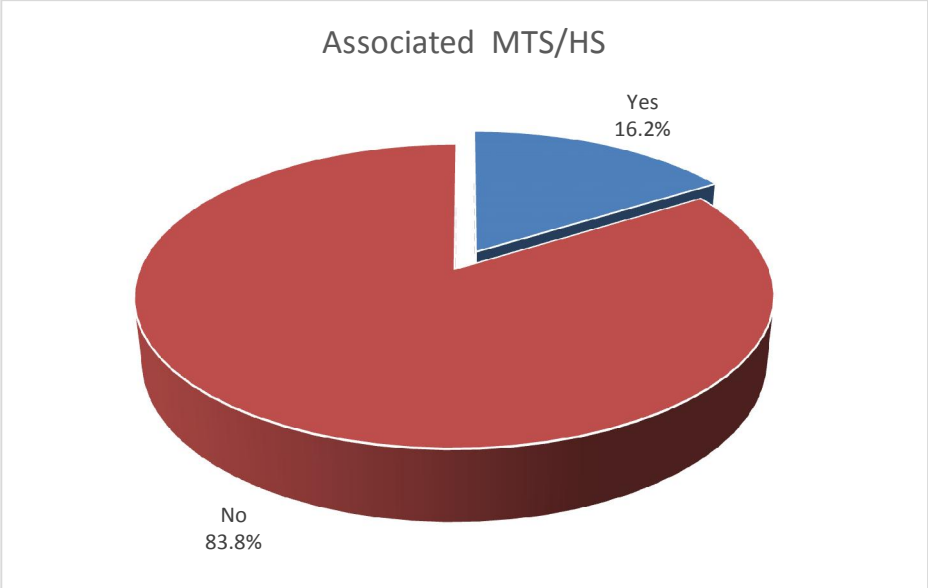

Fig 15

Surgery :

A standard ATL was under-taken for those with mesial and lateral temporal lesions (n=102). In extra temporal lesion lesionectomy was done.

In 29 patients with associated hippocampal sclerosis, an ATL was done in addition to lesionectomy in temporal lesions. If the ECoG showed significant spiking after the resection, a further extension of the resection margins was undertaken

154 patients underwent gross total decompression and 21 patient near total and 4 patient subtotal decompression due to eloquent area of the tumor.(table 15,figure 16)

Surgery	Frequency	Percent
Subtotal	4	2.2
Near total	21	11.8
Gross total	154	86.0
Total	179	100.0

Table 15

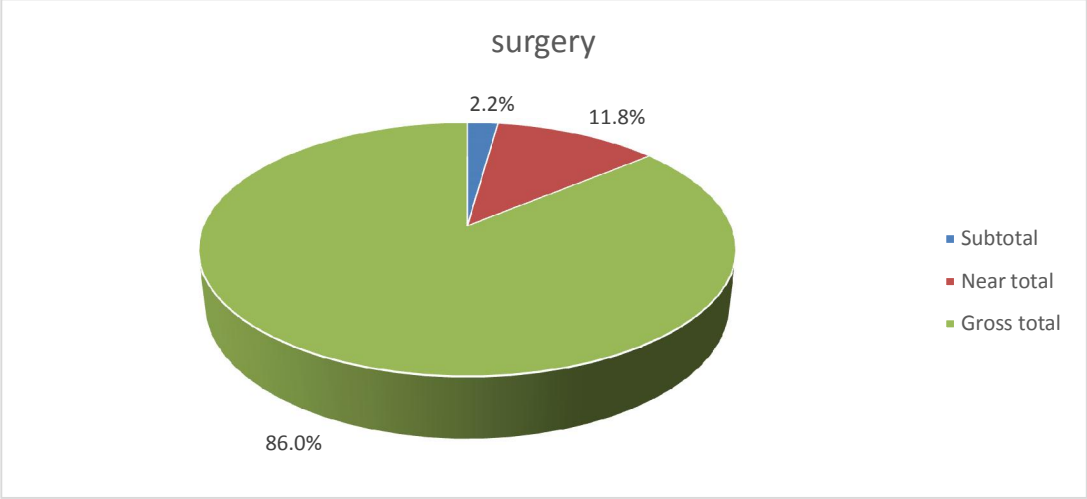

Fig 16:surgical excision types

Post excision EcoG showed no spikes in 79.4% and persistent spiking in 15.6% and inconclusive in 5%(fig 17)

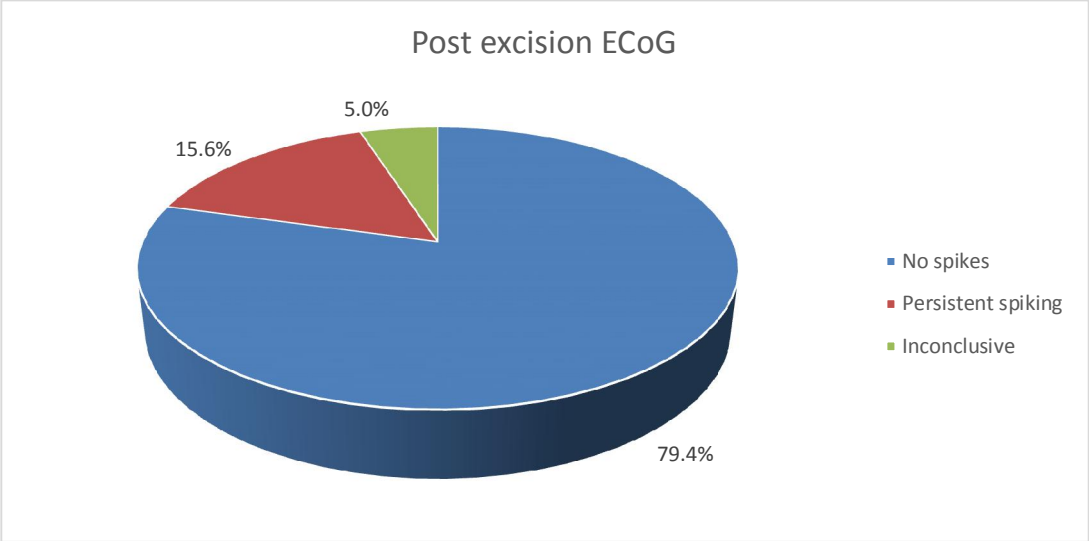

Fig 17

Pathology:

Ganglioglioma was the most common pathology in 96(53.6%), Dysembryoplastic neuroepithelial tumor was noted in 65(36.3%) PXA noted in 6(3.4%) pilocytic astrocytoma in 8 patients(4.5%) Low grade glioma was seen in 4(2.2%) comprising fibrillary astrocytoma, and Angiocentric glioma.None of them showed nuclear atypia, mitosis, necrosis or endothelial proliferation indicating anaplastic change.(table 16 fig 18)

HPR	Frequency	Percent
Ganglioglioma	96	53.6
DNET	65	36.3
PXA	6	3.4
Others	4	2.2
Astrocytoma Grade 1	8	4.5
Total	179	100.0

Table 16

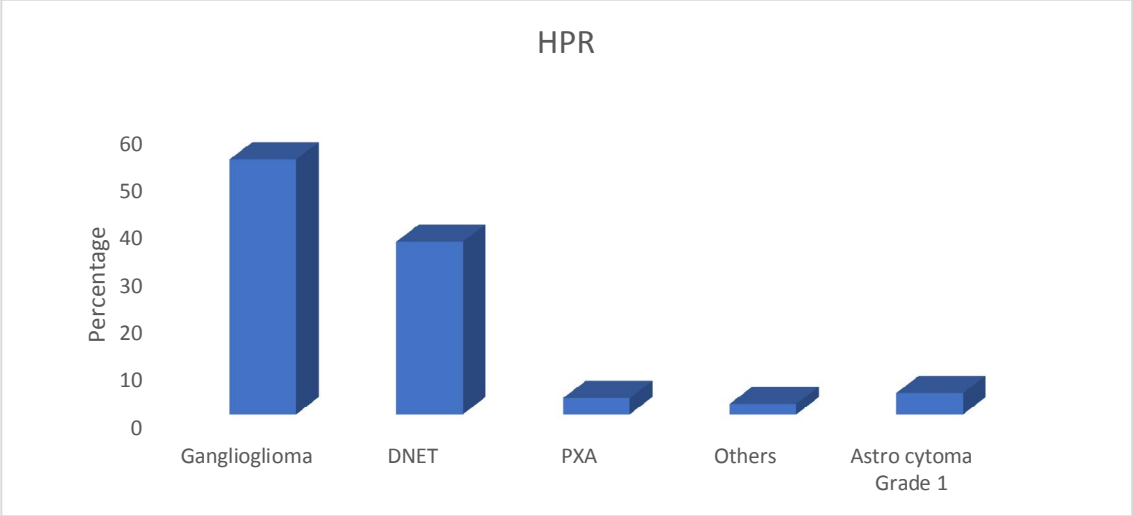

Fig 18

Post operatively 14 patient developed focal deficit 7 patient had hemiparesis which improved and all of them ambulant at one year follow up,1 patient with cingulate gyrus lesion developed ankle weakness with gradually improved,2 patient developed transcortical sensory aphasia with improved with speech therapy,1 patient with chiasmal lesion developed decreased visual acuity, 3 patient with occipital lesion developed hemianopia with no disability in day to day life.(table 17)

Superficial wound infection noted in 6 patient and was managed conservatively with dressing and antibiotics(table 18)

No mortality was noted, none underwent radiation or chemotherapy

FND Post op	Frequency	Percent
Yes	14	7.8
No	165	92.2
Total	179	100.0

Table 17

Wound infection	Frequency	Percent
Yes	6	3.4
No	173	96.6
Total	179	100.0

Table 18

Following operation 24 patients(13.4%)developed acute postoperative seizures within 1 week of surgery(fig 19)

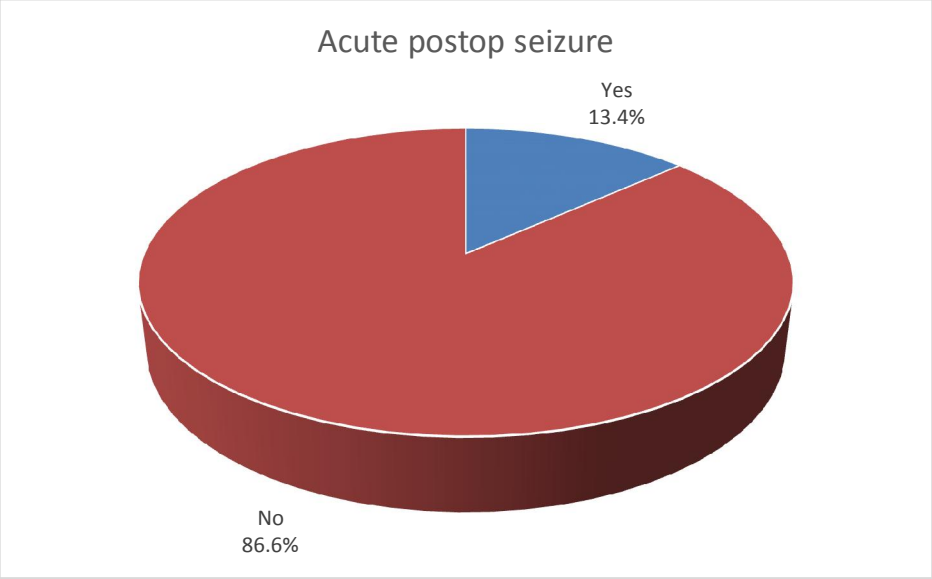

Fig 19

Variables predicting seizure outcome

Mean follow up of 3.1 years 127 patients (70.9)% had excellent and 147 had favourable 82.2% seizure free outcome(table 19,fig 20)

Engel outcome scale	Frequency	Percent
Class I	127	70.9
Class II	20	11.2
Class III	23	12.8
Class IV	9	5.0
Total	179	100.0

Table 19

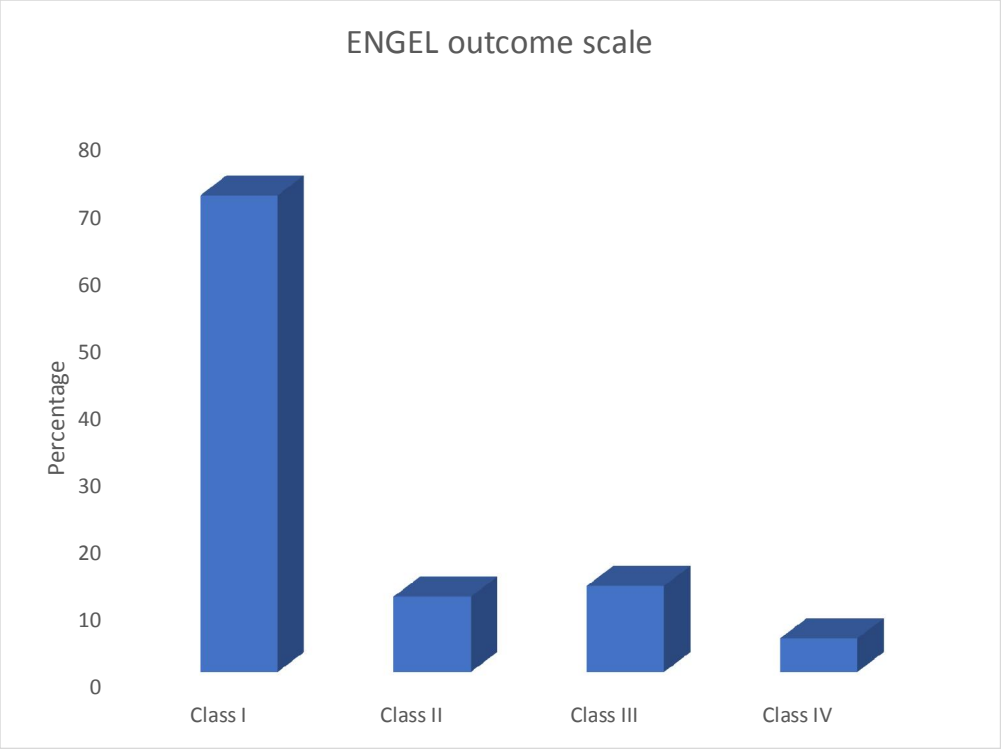

Fig 20

63%weaned of AED at last follow up(table 20)

Stopped AED	Frequency	Percent
Yes	113.0	63.1
No	66.0	36.9
Total	179.0	100.0

Table 20

Univariate analysis

The results of unpaired t-test and Pearson's Chi-square test of factors associated with favorable and unfavorable outcome are depicted in table 21 and table 22 and fig 21)

Male gender(p-0.023) presence of secondary generalized seizures(p-0.006)associated MTS/HS(p-0.043)duration of symptoms (p-0.027)are preoperative factors associated with unfavourable seizures outcome. Subtotal excision(p-0.011) and immediate postop seizure(p-0.007) associated with unfavourable seizures outcome and post resection EcoG with No spikes showed favourable outcome (p-0.023)histopathology wise DNET(p-0.029)associated with unfavourable seizures outcome and Factors like age at seizure onset, age at surgery, side and location of tumor, CT density and calcification and contrast enhancement had no correlation to seizure outcome

	Favorable outcome		Unfavorable outcome			
	mean	sd	mean	sd	t	p
Age	18.97	11.78	21.50	12.92	1.083	0.280
Age at onset of symptoms	11.96	11.21	12.69	12.43	0.326	0.745
Duration of symptoms	82.71	80.80	118.06	82.01	2.236	0.027

Table 21

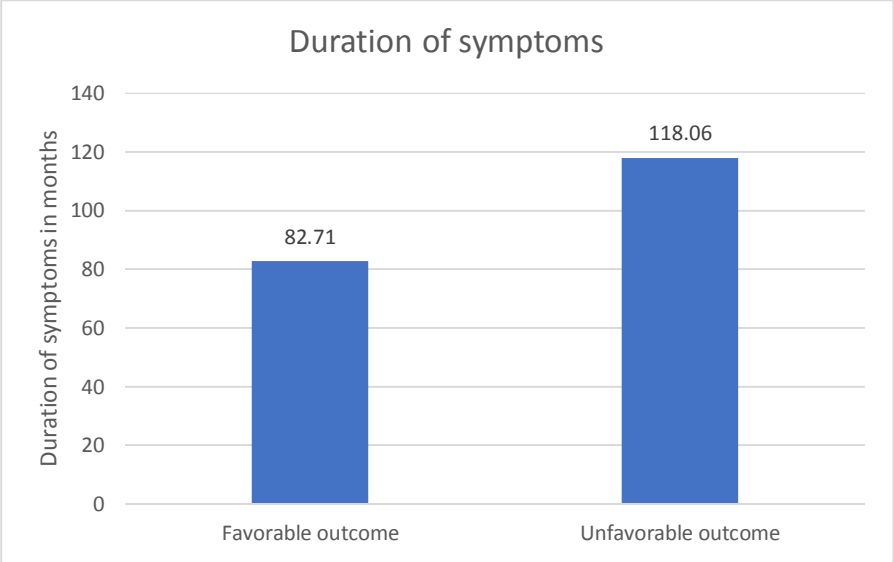

Figure 21

Analysis of different variables with seizure outcome

		Favorable outcome		Unfavorable outcome		Total				
		N	%	N	%	N	%	χ^2	df	p
Gender	Male	83	76.9	25	23.1	108	100			
	Female	64	90.1	7	9.9	71	100	5.153	1	**0.023**
Initial precipitating factors	Yes	13	81.3	3	18.8	16	100			
	No	134	82.2	29	17.8	163	100	0.009	1	0.924
Seizures frequency	1-3	45	88.2	6	11.8	51	100			
	4-5	41	83.7	8	16.3	49	100			
	>5	61	77.2	18	22.8	79	100	2.674	2	0.263
Type of Seizure	Focal	85	89.5	10	10.5	95	100.0			
	Focal with Generalization	49	72.1	19	27.9	68	100.0			
	GTCS	13	81.3	3	18.8	16	100.0	8.196	2	**0.017**
Presence of aura	Yes	88	83.8	17	16.2	105	100			
	No	59	79.7	15	20.3	74	100	0.492	1	0.483
Location of tumor	Temporal	81	80.2	20	19.8	101	100			
	Extratemporal	66	84.6	12	15.4	78	100.0	0.585	1	0.444

side	Right	74	83.1	15	16.9	89	100			
	Left	73	81.1	17	18.9	90	100	0.126	1	0.722
size	<3cm	55	87.3	8	12.7	63	100			
	3-5 cm	76	78.4	21	21.6	97	100			
	>5cm	16	84.2	3	15.8	19	100	2.148	2	0.342
Ct density	Hyperdense	11	78.6	3	21.4	14	100			
	Isodense	79	83.2	16	16.8	95	100			
	Hypodense	44	81.5	10	18.5	54	100			
	Mixed dense	13	81.3	3	18.8	16	100	0.213	3	0.975
Calcification	Yes	47	82.5	10	17.5	57	100			
	No	100	82	22	18	122	100	0.006	1	0.937
Associated MTS/HS	Yes	20	69	9	31	29	100			
	No	127	84.7	23	15.3	150	100	4.081	1	**0.043**
Contrast enhancement	Yes	80	83.3	16	16.7	96	100			
	No	67	80.7	16	19.3	83	100	0.207	1	0.649
surgery	Subtotal	3	75	1	25	4	100			
	Near total	13	61.9	8	38.1	21	100			
	Gross total	131	85.1	23	14.9	154	100	6.893	2	**0.032**
Post excision ECoG	No spikes	122	85.9	20	14.1	142	100			
	Persistent spiking	18	64.3	10	35.7	28	100			
	Inconclusive	7	77.8	2	22.2	9	100	7.575	2	**0.023**
HPR	Ganglioglioma	85	88.5	11	11.5	96	100			
	DNET	48	73.8	17	26.2	65	100			
	PXA	4	66.7	2	33.3	6	100			
	Others	3	75	1	25	4	100			
	Astro cytoma Grade 1	7	87.5	1	12.5	8	100	6.999	4	0.136
Ganglioglioma	Yes	85	88.5	11	11.5	96	100.0			
	No	62	74.7	21	25.3	83	100.0	5.810	1	**.016**
DNET	Yes	48	73.8	17	26.2	65	100.0			
	No	99	86.8	15	13.2	114	100.0	4.762	1	**.029**
Acute postop seizure	Yes	15	62.5	9	37.5	24	100			
	No	132	85.2	23	14.8	155	100	7.269	1	**0.007**

Table 22

Univariate analysis showing variables with significant association

		Outcome				Total				95% CI of OR	
		Bad outcome		Good outcome							
		N	%	N	%	N	%	p	OR	Lower	uppr
Gender	Male	25	78.1	83	56.5	108	60.3				
	Female	7	21.9	64	43.5	71	39.7	0.02	2.75	1.12	6.77
Focal with Generalisation	Yes	19	59.4	49	33.3	68	38				
	No	13	40.6	98	66.7	111	62	0.01	2.92	1.33	6.41
Associated MTS/HS	Yes	9	28.1	20	13.6	29	16.2				
	No	23	71.9	127	86.4	150	83.8	0.04	2.49	1.01	6.13
Subtotal	Yes	9	28.1	16	10.9	25	14				
	No	23	71.9	131	89.1	154	86	0.01	3.20	1.26	8.11
EcoG No spikes	Yes	20	62.5	122	83	142	79.3				
	No	12	37.5	25	17	37	20.7	0.01	0.34	0.15	0.79
Ganglioglioma	Yes	11	34.4	85	57.8	96	53.6				
	No	21	65.6	62	42.2	83	46.4	0.02	0.38	0.17	0.85
Dnet	Yes	17	53.1	48	32.7	65	36.3				
	No	15	46.9	99	67.3	114	63.7	0.03	2.34	1.08	5.08
Acute postop seizure	Yes	9	28.1	15	10.2	24	13.4				
	No	23	71.9	132	89.8	155	86.6	0.01	3.44	1.35	8.79

Table 23

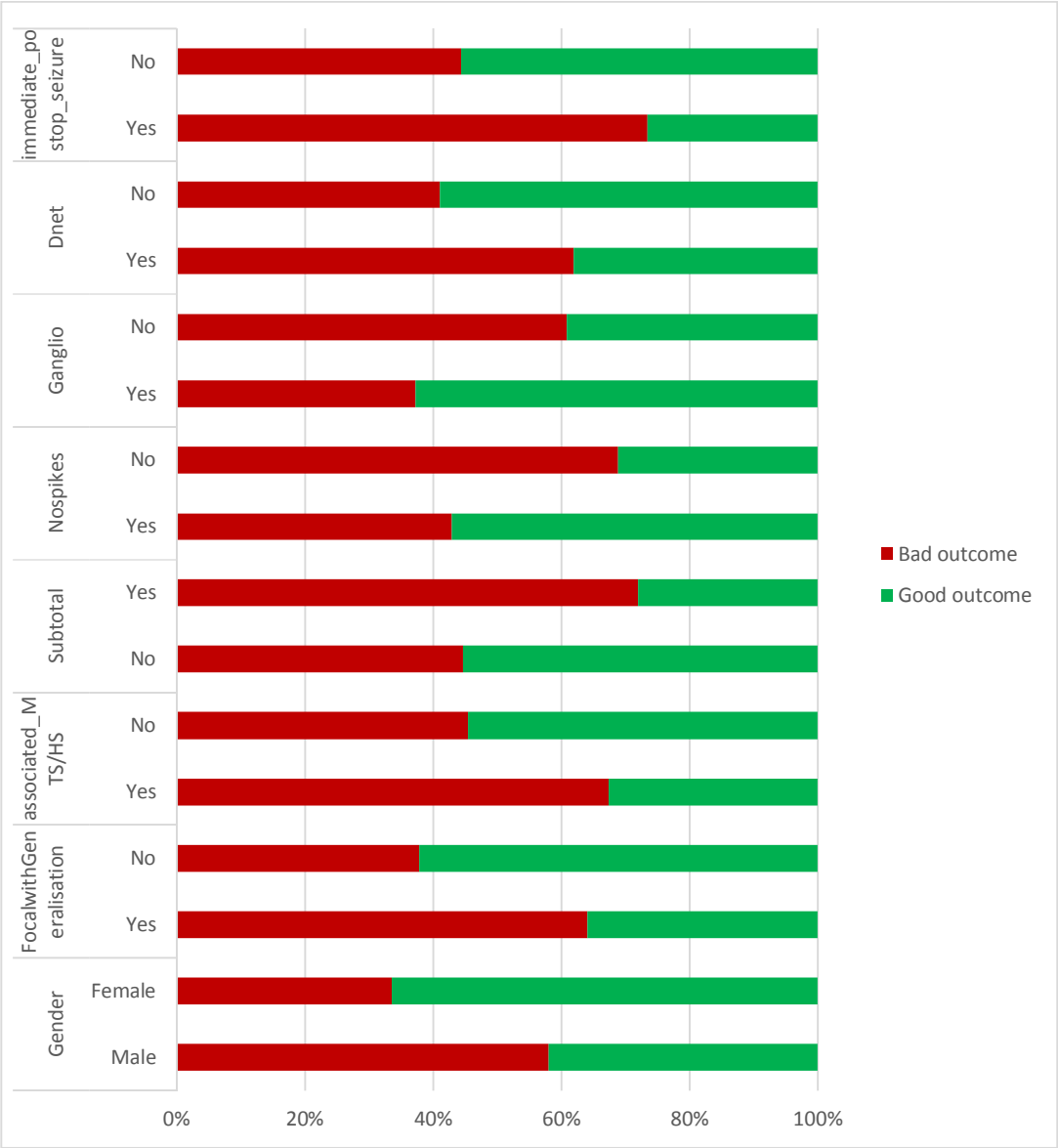

Fig 22

Multivariate analysis

The factors of significance in univariate analysis were carried on to multivariate Cox proportional hazards regression model. (table 24)

Binary logistic regression model for bad outcome

	B	S.E.	Wald	df	p	OR	95% C.I.for OR	
							Lower	Upper
Gender- Male	1.213	1	5.585	1	**0.018**	3.36	1.23	9.204
DNET	1.082	0	5.085	1	**0.024**	2.95	1.15	7.560
Focal with Generalisation	1.237	0	6.713	1	**0.010**	3.44	1.35	8.778
Subtotal excision	1.548	1	6.265	1	**0.012**	4.70	1.40	15.794
Post excision Nospikes	-0.430	1	0.607	1	0.436	0.65	0.22	1.918
Associated MTS/HS	0.786	1	1.941	1	0.164	2.19	0.73	6.628
Acute postop seizure	0.672	1	1.287	1	0.257	1.96	0.61	6.257
Duration of symptoms	-0.004	0	2.165	1	0.141	1.00	0.99	1.001
Constant	-8.216	3	8.254	1	0.004	0.00		

Table 24

Male gender (p value-0.018), DNET(p-0.024), Focal with secondary generalization(p-0.010), Sub total excision(p-0.012) are the independently predictors of bad outcome

Number of patients remaining seizure-free and not seizure-free plotted against the duration of epilepsy prior to surgery shows no significant difference between the group(table 25 ,fig 23)

Duration of symptom	Seizure free survival				Total	
	No		Yes			
	N	%	N	%	N	%
<5 year	14	15.7	75	84.3	89	100.0
6-10 years	10	22.7	34	77.3	44	100.0
11-15 years	4	18.2	18	81.8	22	100.0
15-20 years	4	26.7	11	73.3	15	100.0
>20 years	2	22.2	7	77.8	9	100.0
Total	34	19.0	145	81.0	179	100.0

Table 25

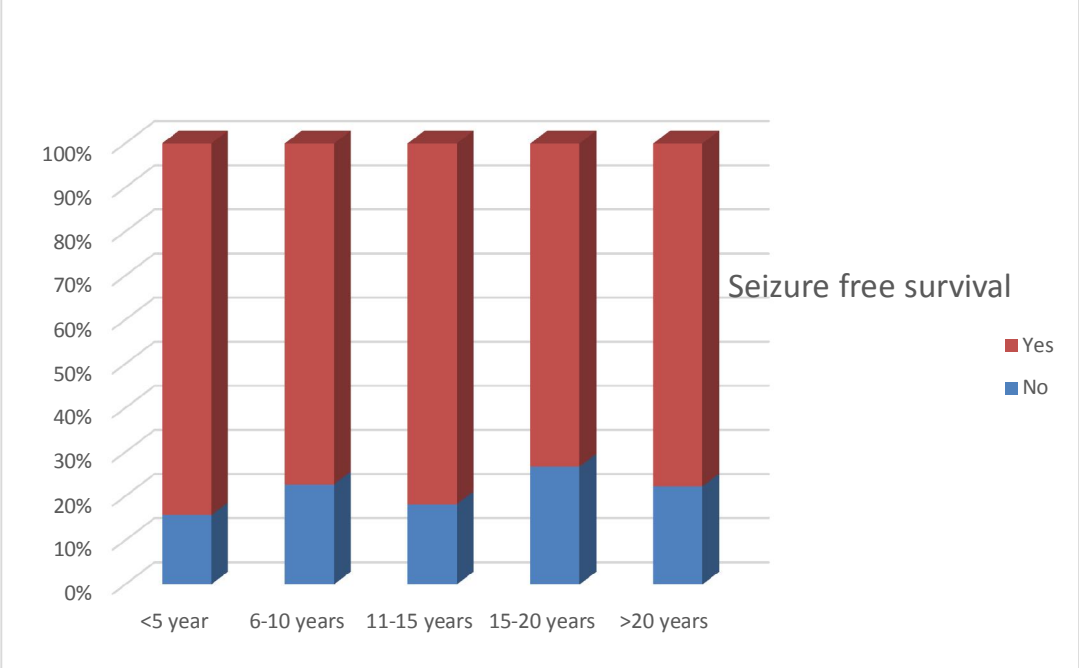

Fig 23

Kaplan–Meier estimates of the probability of cumulative mean seizure-free survival in years and time taken for relapse of seizures for the subtotal vs total shows subtotal has unfavourable seizure free survival (fig 24)and ganglioglioma versus DNET (fig 25)shows DNET having poor seizure free survival rates

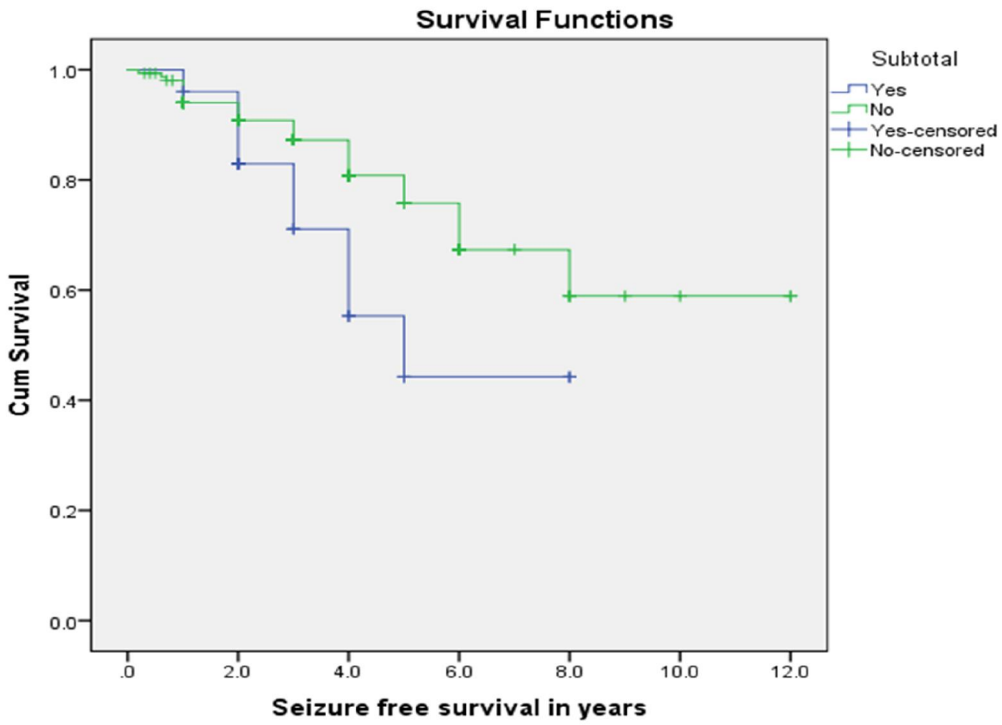

Fig 24 Kaplan–Meier estimates for seizure free survival for subtotal excision

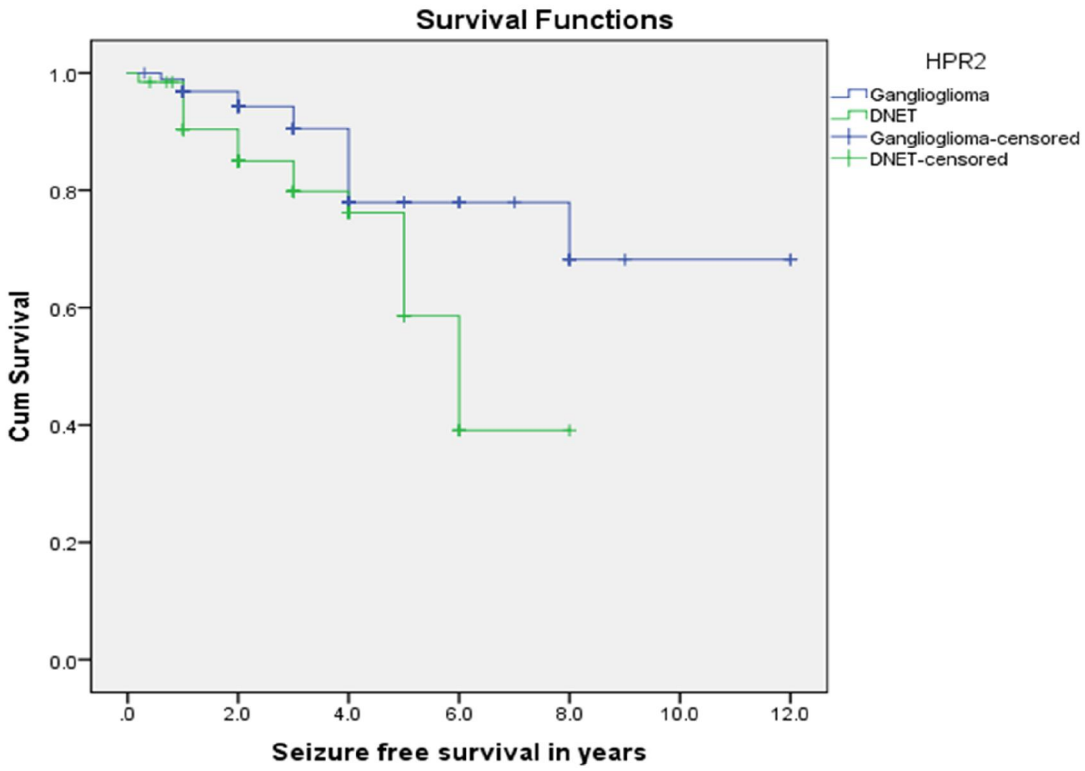

Fig 25 Kaplan–Meier estimates for seizure free survival for DNET vs GG

DISCUSSION

DISCUSSION

Epilepsy surgery is an effective therapeutic option for patients with Long term epilepsy associated tumors (LEATs), which are now frequently diagnosed early as a result of the advances made in neuroimaging techniques and increasingly extensive experience in discovering anatomoelectroclinical correlations. Studies of epilepsy surgery stress the importance of early interventions because of their beneficial effects on seizures and cognitive development.[72] [73] However, it is still not clear when the optimal time is for surgery, as can be seen from the variability in the mean epilepsy durations reported in the literature.[4] [74] With the concept of surgically remediable epilepsy syndromes introduced by Engel and Shewmon(1995),early surgical referrals are advocated for lesions that cause significant epilepsy associated morbidity and have good surgical outcome.LEATs are included in these surgically remediable epilepsy syndromes.

There is a paucity of published literature on Long term epilepsy associated tumors (LEATs) from Indian epilepsy centres. In this study, we present a long-term follow-up of a large series of glioneuronal tumors from a large volume tertiary epilepsy care centre, R Madhavan Nair Centre for comprehensive epilepsy care, Trivandrum, India. Our study would be one of

the largest homogeneous cohort of LEATs causing refractory seizures encountered.

Similar series from our centre by Radhakrishnan et al. [75] with 105 patient showed that more than 70% of patients become completely seizure-free in long term in LEATs after surgery. This study expands the cohort with nearly double the number of patients included and further longer postoperative follow up of patient

Demographic profile:

In our study we found male dominance 60.3% which was in accordance with previous studies[76]

The tumors in our cohort showed a predilection for younger age of onset with a mean age of onset 12.1+11.4 which was in accordance with previous studies[77] [61].

Gender: Previous studies comparing gender with seizure outcome does not show any significant correlation [75] [1] [78]Our findings of a sex difference in outcome (worse outcome in men compared with women) do not have a clear explanation.(table 24) There is paucity in literature regarding this and studies found that male animals were more prone to seizure activity than were female animals.[79] In humans, men may be more susceptible to temporal lobe–like seizures because of high levels of testosterone[79] and more vulnerable to seizure associated brain damage and may have a slightly higher overall incidence of epilepsy when compared with women,[80] On the

other hand, greater plasticity has been found in women when compared with men, in terms of memory, in response to the onset of epilepsy. Cortical gray matter differences are modulated by androgen receptor genotyope and by circulating levels of hormones. Gray matter volumes tend to follow inverted U shaped trajectories with peak size occurring earlier in females. White matter volumes become increasingly divergent as males and females reach adulthood. As brain regions growing at different rates between males and females the magnitude or even direction of the difference depends on the age at which measurements are made[81]

Sex differences in seizure recurrence after surgical treatment of LEAT have not been shown to be a predictive factor, but most of the previous analyses have included smaller samples than our study did, or simply sex was not considered as a variable under study.

Tumor location

In agreement with the literature, tumors in our series are usually located in the temporal lobe (fig 14) and MRI appears to be more sensitive in identifying LEATs than CT scans (Castillo et al., 1990; Haddad et al., 1992; Zentner et al., 1994). However, CT or MRI features appear not to have a detectable influence on the postoperative seizure outcome. It is likely that the inherent epileptogenicity of structures in the mesial temporal lobe contributes to seizure generation in this region (Delgado-Escueta et al., 1986; Engel et al., 2009).

Symptom profile

The most common presenting symptom of glioneuronal tumors is represented by seizures, with an incidence rate in the literature of 70–100% (Kalyan-Raman and Olivero, 1987; Daumas-Duport et al., 1988; Silver et al., 1991; Haddad et al., 1992; Pilcher et al., 1993; Hakim et al., 1997). In our series, 92% of the patients have, as only presenting symptom, seizures, which are predominantly represented by complex partial seizures resistant to conventional AEDs.

Duration of symptoms:

Previous systematic reviews have shown that a shorter duration of epilepsy predicts improved seizure outcomes in patients with gangliogliomas[52] and low-grade gliomas.[82] A recent literature meta-analysis about epileptogenic gangliogliomas in adult showed that an early surgical intervention of less than 3 years from the onset of seizure is significantly associated with improved seizure control[83]

Some authors observed improvement of seizure outcome in young patients whereas others found no correlation with age at the time of surgery[61 84 85]

Moreover, a number of studies have found that epilepsy duration is not predictive of a good outcome in patients with temporal lobe epilepsy.[86],[87] It is therefore not surprising that the so-called right time to treat LEATs surgically is still an open and highly debated question.

However in our study in univariate analysis it was predictive of good outcome with significant p value but in further multivariate analysis it was not significantly associated with seizure free survival.(fig 21 and fig 23)

Better seizure outcome, however, is observed in patients with shorter duration of epilepsy independently from the age of onset, as well as the age at surgery, suggesting that not only children but also adults may benefit from a relatively early tumor resection, soon after seizure onset[62]. The unfavorable outcome observed in patients with long symptom history could be related to additional epileptogenic mechanisms in perilesional areas. Accordingly, strong expression of the gap–junction protein connexin 43 was found in reactive perilesional astrocytes from patients with longer duration of epilepsy (Aronica et al., 2000).

Recent study by Yang et al(2011)found that early surgical intervention on clinical outcome in ganglioglioma had good outcome when operated within 3 years of symptom onset[83]

An early intervention may also be important in relation to the malignant transformation of these tumors. Accordingly, those patients in which a primary GG underwent malignant change have older age at operation, as well as older age at the time of first symptom.

But longer duration of symptoms is common in poor resource country with few tertiary epilepsy care center and long waiting list for surgery and late

referral, and despite the hypothesis of early surgery and good outcome these patient still have good prognosis according to our analysis

Extent of resection and EcoG :

Another crucial point is the extent of the resection, which is probably essential when considering postsurgical outcomes. It is well known that in patients with tumor-associated epilepsy the extent of tumor resection correlates with improved survival, as well as with the chances of postoperative seizure control.[83] [72] [88] In our series, the association between seizure recurrence and the presence of a postoperative tumor remnant shows a trend toward significance,and the probability of unfavorable outcome is almost twofold when the tumor resection is incomplete(fig 16) Previous studies had indicated the same findings, irrespective of the pathology type (Paolicchi et al., 2000; Terra-Bustamante et al., 2005). Furthermore, complete lesion removal correlated with better seizure outcome in children with tumor-associated epilepsy (Kim et al.,2001)

Some investigators consider the simple resection of the tumor alone sufficient for good seizure control (Daumas-Duport et al.,1988; Morris et al., 1998,[89] whereas others have suggested that the additional resection of epileptogenic zones adjacent to the tumor optimizes seizure outcomes.[90] [91] [77] [92] In our study, the presence of a residual tumor (as a result of a subtotal resection) is associated with poor seizure control in LEAT. Since residual LEAT is also observed in tumors that undergo malignant progression, the

complete extirpation of the tumor appears to be the most appropriate treatment for optimal clinical outcome. Moreover, in temporal lobe tumors, the inclusion in the resection of mesial structures improved the seizure control. A complete and extensive resection implies the necessity of a careful presurgical evaluation, surgical planning and patient counselling.

Surgical data show that complete resection of the solid tumors and immediately adjacent tissue harboring satellites may disrupt epileptogenic networks and lead to high rates of seizure freedom, challenging the epileptogenic relevance of more extensive adjacent dyslaminated cortex. Whether the latter is a primary or secondary abnormality and whether dyslaminated cortex in the context of a second lesion may produce seizures after complete resection of the main lesion is still to be proven

LEAT and focal cortical dysplasia FCD are common findings in drug-resistant focal epilepsies, and frequently coexist[29 30]. Rarely MRI features of LEAT could be misinterpreted as FCD. So to know the surrounding area of electrical activity and guide and achieve gross total resection we have used intraoperative EcoG and resection was tailored to presence of spikes or not and our study showed significant association between absent post resection spikes with favourable outcome in univariate analysis which is in accordance to previous studies[93]

Seizure outcome:

Our results are in agreement with other surgical series where 70–80% gain complete seizure freedom following surgery for tumors [9495] [96]. our study report a long term seizure control in LEAT with 71% of patient with Engel outcome class I .Seizure control is remarkably stable over several years. The probability of remaining seizure-free for patients with glioneuronal tumors who are seizure- free for at least the first 2 years after surgery is 97%, suggesting that the long-term outcome can be predicted 2 years after surgery. This is in agreement with a recent study concerning intractable temporal lobe epilepsy induced by differ- ent causes, including brain tumors (Salanova et al., 1999). A recent systematic meta analysis of 773children and adults examined factors predicting seizure freedom after low grade glioma surgery and found that gross total resection, good pre-operative seizure control, and duration of seizures of one year or less predicted better outcome[72]

Secondary generalized seizures:

Secondary generalized seizures prior to surgery was the single predictor of a poor post-surgical outcome..

In data by Radhakrishnan et al on refractory extratemporal epilepsies encompassing all lesions including tumors, preoperative secondary generalized seizures caused a less favorable outcome after surgery[92]. In a multicentre prospective study on resective epilepsy surgeries (temporal and

extratemporal), Spencer et al. (2005). observed that a lack of preoperative secondary generalized seizures was the only attribute that predicted postoperative seizure-free outcome [97]. The same was observed by Jansky et al. (2005) in cases of temporal lobe lesions, those with pre-operative generalized seizures had less favourable seizure outcome [98]. Secondary generalized seizures implies secondary epileptogenesis and/or mirror foci, there have been few series supporting this view[9354]. Our study is in accordance with these studies with a significant association and independent predictor of bad seizure outcome in multivariate analysis.

The presence of secondarily generalized seizures has been associated with more significant mesial temporal atrophy (Cook et al., 1992; Cendes et al., 1994). It is, therefore, plausible that tumor patients with secondarily generalized events have higher rates of dual pathology (Fish & Spencer, 1995; Spencer & Huh, 2008), which may continue to drive seizures after lesionectomy.In study done by englot et al[99]observed significantly higher rates of seizure-freedom with extended resection (including hippocampectomy)in patients with temporal lobe glioneuronal tumors, suggesting that dual pathology may contribute to ictogenicity in these lesions.

DNET vs other lesion:

Other studies of LEAT comparing DNET with other tumor and seizure outcome doesn't not show any significant correlation[100 64 75] but our study show DNET is associated with significant poor seizure outcome (fig 25)

Poorer seizure outcomes in patients with DNET may also be associated with DNET recurrence, presence of cortical dysplasia,[101] incomplete resection of lesions or adjacent dysplastic tissue, and the presence of cognitive problems and developmental delay. The latter may reflect widespread dysplastic areas accompanying the DNET and causing disturbances in neuronal circuitry.[102 100] GABA-mediated synaptic inhibition in malformations of cortical development could be secondary to reductions in GABA transporter expression or changes in the expression and/or function of specific GABA receptor subtypes. Aronica et al suggest that the cellular distribution of components of the GABAergic system in DNET, together with the perilesional changes, suggests that alterations of the GABAergic system may contribute to the complex abnormal functional network of these highly epileptogenic developmental lesions.

Acute post operative seizures:

In our study there was 24 cases (13.4%)(fig 19)of seizures occurring immediate post operative period or within one week of surgery and was associated with poor outcome in univariate analysis but in multivariate analysis it was not significant. Similar study in relation to temporal lobe

lesion and seizure outcome showed strong predictor of later seizure recurrence[80].

Some studies reported that seizures occurring during the early postoperative period are not associated with poor long-term outcome[103]. It has been suggested that these seizures, often of focal motor type or GTCS and named ‘‘neighborhood seizures’’, may result from the effects of acute surgical injury. On the other hand, several studies found a significant association between postoperative seizures and Temporal lobe lesion surgery failure, especially when they were semiologically similar to patient's habitual seizures.[103] Garcia et al.1 reported that post operative seizure, which occurred in 27 (49%) of 55 pediatric and adult patients who underwent temporal lobectomy, were associated with a poor outcome only if there was more than one event and it occurred more than 24 h after surgery

Associated hippocampal sclerosis:

In our study we found 16.2% (fig 15)of patient population had MTS/HS in neuroimaging and was found to have bad outcome in univariate analysis but multivariate analysis didn't show any significant association with seizure outcome ,the reason for association may be due to secondary epileptogenesis or concept of mirror focus(MF) Secondary epileptogenesis is the concept that an actively discharging epileptogenic region may provoke similar paroxysmal activity in regions distant to the original site. The MF is the special case of secondary epileptogenesis in which activity is

provoked in homologous cortex[93]. Spikes are initially dependent and linked temporally to spikes in the primary lesion, with further passage of time spikes may develop in contralateral homotopic cortex that are not temporally linked to the discharging primary focus. These contralateral spikes, which have been termed a mirror focus, then occur asynchronously and reflect a fundamental change in the underlying excitability of that homotopic cortex. If ablation of the primary cortex is performed at this stage, the contralateral spike will ultimately disappear. However, if the primary lesion remains undisturbed, later excision of the primary lesion may not abolish the interictal spikes in homotopic cortex. The contralateral spikes may then be considered as independent, and this stage probably represents a fundamental change in the character of the secondary lesion . As the process progresses further, recurrent seizures may arise from that contralateral homotopic focus, which has become a fully independent cause of epilepsy[104] . Contralateral focus has several possible explanations. It could be due either to another primary brain abnormality related or unrelated to the obvious lesion, to brain injury directly caused by seizures (e.g., anoxia or head trauma), or secondary epileptogenesis. (e.g., hippocampal sclerosis) exists on neuroimaging[105].

Literature review of seizure outcomes in patients treated surgically for LEAT compared to present study shows a similar favourable outcome with our study having larger cohart and long follow up (table 26)

Authors and year	No of pts	Mean FU(years)	%Engel Class I
Fomekong et al,1999	16	3.2	53.3
lee et al,2000	20	3.2	90
Aronica et al,2001	20	5.0	58.0
Luyken et al 2003	25	8.0	86.0
Nolan et al ,2004	26	4.3	62
Chan et al,2006	18	1.6	66.7
Sharma et al 2009	32	2.5	100
Radhakrishnan et al	105	7.5	74.2
Present study	179	3.1	70.9

Table 26

Major series (cohort of $\geq$ 50 patients) addressing Long-term Epilepsy-Associated Tumor (LEAT) and its predictors after resective surgery (table 27)

Series, year	Number of patients	Predictors of good seizure outcome	Remarks
Zaatreh, 2003 [12]	68	Completeness of resection	- Only temporal lobe tumors - 10%-comprised of high grade tumors heterogeneous cohort) - 87% became seizure-free
Radhakrishnan 2015	105	-Absence of secondary generalized seizure -extra temporal tumor location -preoperative duration of epilepsy less than 6 years	-74% became seizure free -long follow up of 7.5 years
Giulioni et al 2017	339	-Temporal location -Absence of secondary generalization -Completeness of excision	-Data from 8 different centers -89% seizure free -Shorter duration of study
Present study	**179**	- Absence of secondary generalized seizure -female gender - Completeness of excision	-largest cohart from single institute -70.9% became seizure free -DNET carried bad prognosis

Table 27

Limitation of the study:

Present study is retrospective study and is limited by its inherent drawbacks, there is a chance for selection bias and chance of patient losing for follow up and since follow up done by multiple observer there is a chance for interobsever bias .Other limitation include, in our study Engel subset scoring was not applied or ILAE score was not used.and since mean duration of follow up was 3.1 years in our study further follow up would be ideal to assess surgical failure and malignant progression and long term prospective trial would be ideal to overcome these limitation

CONCLUSION

CONCLUSION

This study concludes that surgical treatment of LEATs irrespective of preoperative responsive to anti-convulsant drugs contributes significantly to seizure control. Seventy percent of patients are completely seizure free and more than 50% of them become medication free in the long term with no surgical mortality and negligible morbidity.

For a good postoperative seizure outcome, the optimal surgical treatment of patients with LEATs is complete resection of the tumor. It may be useful to have intraoperative ECoG in all patients with LEATs due to the high likelihood of finding a dysplastic cortex,resection of which without further neurological deficits,improves seizure outcome. The duration of epilepsy and age at surgery did not significantly influence the patient prognosis.In pre-operative seizure semiology,secondary generalization caused less favourable seizure outcome after surgery and DNET is associated with bad outcome compared with other LEATs.

ABBREVIATIONS

LEAT	long-term epilepsy associated tumor
DNET/DNT	Dysembryoplastic neuroepithelial tumors
GG	Ganglioglioma
GNT	Glioneural tumor
ILAE	International League Against Epilepsy
EcoG	Electrocorticography
BBB	Blood brain barrier
ADK	adenosine kinase
FCD	focal cortical dysplasia
CPS	complex partial seizure
MF	mirror focus
ANT	angiocentric glioma
ISO	isomorphic astrocytoma variant
PA	pilocytic astrocytoma
PXA	pleomorphic xantoastrocytoma
OLIGO	oligodendroglioma
AKT	akt murine thymoma viral oncogen
DEPTOR	DEP domain containing MTOR-interacting protein
FOS	FBJ murine osteosarcoma viral oncogene homolog
GRB2	growth factor receptor-bound protein 2
INSR	insulin receptor
MAPK	mitogen-activated protein kinase
MTOR	mechanistic target of rapamycin
PI3K	phosphoinositide-3-kinase,
NRAS	neuroblastoma
RHEB	ras homolog enriched in brain
SOS1	son of sevenless homolog 1
STAT-	signal transducer and activator of transcription
TSC	tuberous Sclerosis

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APPENDIX - I

PATIENT PROFORMA

Sree Chitra Tirunal Institute for Medical Sciences & Technology

Proforma "Post surgical outcome of Long Term Epilepsy associated tumors (LEAT): A retrospective cohort study"

A. GENERAL INFORMATION

Anonymized Patient ID:

Age

Gender

B.CLINICAL DETAILS

Age at onset of habitual seizures(Years)

Duration of epilepsy prior to surgery(Years/Months)

History of initial precipitating injury(Yes/No)

Any associated psychiatric comorbidities(Yes/No)

Seizures types: aura/CPS/Any GTCS

Presence of neurological deficit: hemianopia/dysarthria/cortical sensory loss

Concordant/discordant EEG

Invasive monitoring: (Yes/No)

Size of tumor(mm):

Extent of tumor:

Location of tumor:lobar/multilobar

Lobe involved

Contrast enhancement: (Yes/No)

Gliosis/associated hippocampal sclerosis/calcification(Yes/No)

C. INTRAOPERATIVE EVENTS

Intra-operative extent:

Gliosis/associated hippocampal sclerosis:

Duration of surgery:

Intraop EEG spikes:

D. POST-OPERATIVE EVENTS

Seizures:

Infection:

A.Wound:superficial/deep

B.Systemic

Fresh post op deficit

CSF leak:

Meningitis:

Post op EEG spikes:

Number and dose of antiepileptic

Post op imaging

Extent of excision

E. STATUS ON DISCHARGE

Frequency of Seizures(Engel score)

Post op EEG spikes

Motor and speech status

Any other deficit

Number and dose of antiepileptic

Histopathology

F. STATUS ON FOLLOW UP ON 6 MONTHS

Seizures

Post op EEG spikes

Motor and speech status

Any other deficit

Number and dose of antiepileptic

Radiological follow up

G. STATUS ON FOLLOW UP ON 1 YEAR:

Frequency of Seizures

Post op EEG spikes

Motor and speech status

Any other deficit

Number and dose of antiepileptic

Radiological follow up

H.STATUS ON FOLLOW UP ON 1.5 YEAR:

Frequency of Seizures

Post op EEG spikes

Motor and speech status

Any other deficit

Number and dose of antiepileptic

Radiological follow up

I. STATUS ON FOLLOW UP ON LAST FOLLOW UP:

Duration:(months)

Frequency of Seizures/Post op Engel score)

Post op EEG spikes

Motor and speech status

Any other deficit

Number and dose of antiepileptic

Radiological follow up

APPENDIX - II

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

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

SCT/IEC/1068/OCTOBER-2017 25.10.2017

Dr. Pradeepanand Vaidya
Senior Resident
Department of Neurosurgery
SCTIMST, Thiruvananthapuram

Dear Dr. Pradeepanand Vaidya,

The Institutional Ethics Committee reviewed and discussed your application to conduct the study entitled "POST SURGICAL OUTCOME OF LONG TERM EPILEPSY ASSOCIATED TUMORS (LEAT): A RETROSPECTIVE COHORT STUDY (IEC/1068)" on 21st October, 2017.

The following documents were reviewed:

1. *Covering letter addressed to the Chairperson, IEC, SCTIMST dated 04.08.2017 with check list*
2. *TAC Approval Letter*
3. *Copy of IEC Recommendation Letter dated 06.07.2017*
4. *IEC Application Form*
5. *Project Proposal*
6. *Proforma*
7. *CV of Principal Investigator and Co-Principal Investigators*

The following members of the Ethics Committee were present at the meeting held on 21st October, 2017 at G. Parthasarathi Board Room, AMCHSS, SCTIMST

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. R V G Menon	M Tech, PhD	Male	Lay Person (Chairman)	No
2.	Dr. Lekha Pandit	MD.DM Neurology, PhD (Bioscience)	Female	Clinician	No
3.	Dr. Kala Kesavan. P	MBBS, MD	Female	Basic Medical Scientist	No
4.	Dr. Rema M. N	MD	Female	Basic Medical Scientist	No
5.	Dr. S S Giri Sankar	LL.M. Ph.D.	Male	Legal Expert	No
6.	Dr. Aneesh V Pillai	BA. LLB (Hons.), LLM, Ph. D, SET (Law)	Male	Legal Expert	No
7.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
8.	Dr. P. Manickam	BSMS, MSc (Epid).,PhD	Male	Health Science Expert/ Social Scientist	No
9.	Dr. Christina George	MD Psychiatry	Female	Clinician	No
10.	Dr. K R S Krishnan	M.E., Ph.D.	Male	Medical Technology	Yes
11	Dr. Harikrishnan S	MD, DM (Cardiology) DNB (Cardiology)	Male	Clinician	Yes
12.	Dr. Mala Ramanathan	PhD	Female	Social Scientist (Member Secretary)	Yes

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,

Mala Ramanathan
Member Secretary, IEC

APPENDIX - III

Plagiarism Checker X Originality Report

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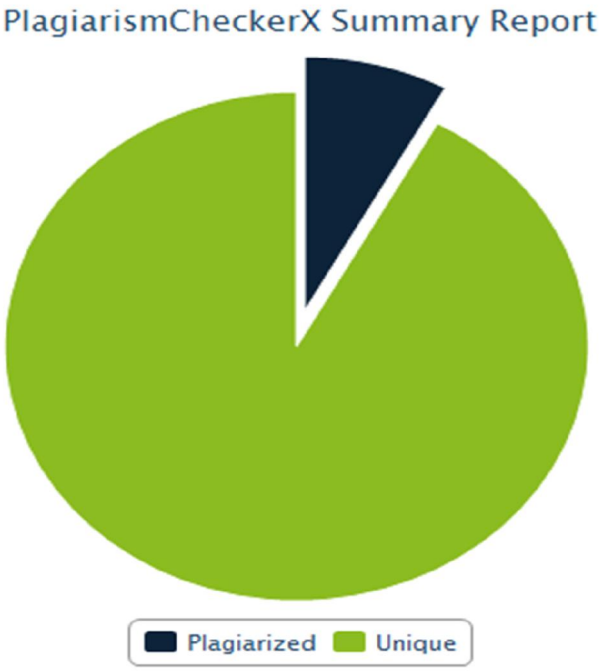

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Slno	hospital_number	Age	AgeSurgery	survival	age_at_onset_of_symptoms	duration_of_symptoms	dos	last_follow_up_date	AEDstoppedaftersxmonths	initial_precipitating_factors	seizures	FND	raised_ICP	others	seizures_frequency	Type	presence_of_aura	location_of_tumor	side	size	ct_density	calcification	associated_MTSHS	contrast_enhancement	surgery	post_excision_ECoG	HPR	wound_infection	FND_A	immediate_postop_seizure	@6month_seizure	@1_year	@1.5_year	last_follow_up_seizure	post_op_recurrance	engeloutcomescale	death	Excellentoutcome	IOCATTION2	Outcome	Gender	Ganglio	Dnet	FocalwithGeneralisation	Subtotal	Nospikes	Durationsymptoms
1	181056	37	33.00	4.0	37.0	0.25	1998	2002.0	12	2	2	1	2	1	2	1	1	3	2	2	2	1	2	1	2	2	1	2	2	2	2	2	2	1	2	1.00	2.00	2.00	1	1.00	2.00	2.00	1.00	2.00	1.00
2	184996	7	3.00	4.0	7.0	2.00	1999	2003.0	36	2	1	2	2	2	1	3	2	2	2	2	3	2	2	2	4	1	1	2	2	2	2	2	2	2	1	2	1.00	2.00	2.00	1	1.00	2.00	2.00	2.00	1.00	1.00
3	9400246	15	13.00	2.0	6.0	144.00	2005	2007.0	0	2	1	2	2	1	3	2	1	1	2	2	4	2	1	1	4	2	1	2	2	1	1	1	1	1	4	2	2.00	1.00	1.00	2	1.00	2.00	1.00	2.00	2.00	3.00
4	193410	12	7.00	5.0	10.0	2.00	2001	2006.0	0	2	1	2	2	2	2	3	2	1	2	2	3	2	2	2	3	2	2	2	2	2	1	1	1	1	1	4	2	2.00	1.00	1.00	1	2.00	1.00	2.00	1.00	2.00	1.00
5	195402	19	15.00	4.0	10.0	108.00	2005	2009.0	24	2	1	2	2	2	2	1	1	2	2	2	1	2	2	2	4	1	2	2	2	2	2	2	2	2	1	2	1.00	2.00	2.00	1	2.00	1.00	2.00	2.00	1.00	2.00
6	39783	15	9.00	6.0	1.0	180.00	2002	2008.0	85	2	1	2	2	2	1	1	1	1	2	2	4	1	1	1	4	1	1	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	1	1.00	2.00	2.00	2.00	1.00	3.00
7	9798273	15	11.00	4.0	12.0	60.00	2002	2006.0	0	1	1	2	2	2	1	1	1	5	2	2	1	2	1	2	3	3	1	2	2	2	1	1	1	1	3	2	2.00	2.00	1.00	1	1.00	2.00	2.00	1.00	2.00	1.00
8	187097	18	14.00	4.0	12.0	72.00	2002	2006.0	36	2	1	2	2	3	2	2	1	1	1	2	4	1	2	1	3	1	1	2	2	2	1	2	2	2	1	2	2	2.00	1.00	2.00	2	1.00	2.00	1.00	1.00	1.00	2.00
9	199461	37	32.00	5.0	36.0	12.00	2002	2007.0	0	2	1	2	2	2	1	2	1	1	2	2	2	2	2	2	4	3	2	2	2	2	2	2	2	1	2	2	2	2.00	1.00	2.00	2	2.00	1.00	1.00	2.00	2.00	1.00
10	207718	50	46.00	4.0	48.0	24.00	2002	2006.0	99	2	1	2	2	2	1	3	2	2	2	2	4	1	2	2	4	3	2	2	1	2	2	1	1	1	2	2	2	2.00	2.00	2.00	2	2.00	1.00	2.00	2.00	2.00	1.00
11	212377	6	0.10	6.0	4.0	24.00	2003	2009.0	60	1	1	2	2	2	3	2	1	6	1	2	4	2	1	2	4	3	2	2	1	1	2	2	2	2	2	1	2	1.00	2.00	2.00	1	2.00	1.00	1.00	2.00	2.00	1.00
12	199998	8	2.00	6.0	9.0	84.00	2002	2008.0	36	2	1	2	1	2	1	2	2	2	1	2	4	1	2	1	4	2	1	2	2	2	2	2	2	2	1	2	1.00	2.00	2.00	2	1.00	2.00	1.00	2.00	2.00	2.00
13	199977	58	54.00	4.0	58.0	2.00	2002	2006.0	48	2	1	2	2	2	1	1	2	2	2	2	1	2	2	2	4	1	1	2	2	2	2	2	2	2	1	1	2	1.00	2.00	2.00	1	1.00	2.00	2.00	2.00	1.00	1.00
14	201364	40	32.00	8.0	40.0	4.00	2002	2010.0	36	2	1	2	2	2	1	3	2	2	2	2	3	2	2	2	4	1	1	2	2	2	2	2	2	2	1	1	2	2.00	2.00	2.00	2	1.00	2.00	2.00	2.00	1.00	1.00
15	202149	22	20.00	2.0	12.0	120.00	2002	2004.0	0	2	1	2	2	2	3	2	1	1	1	2	1	1	2	1	3	1	1	2	1	2	1	2	2	2	2	2	2	2.00	1.00	2.00	1	1.00	2.00	1.00	1.00	1.00	2.00
16	9705725	53	50.00	3.0	47.0	72.00	2002	2005.0	0	2	1	2	2	2	2	1	2	2	1	1	3	2	2	1	3	1	1	2	2	2	2	2	1	1	1	3	2	2.00	2.00	1.00	1	1.00	2.00	2.00	1.00	1.00	2.00
17	208454	30	27.00	3.0	29.0	6.00	2003	2006.0	12	2	2	2	1	4	2	3	2	7	2	2	3	2	2	2	3	1	1	2	2	2	2	2	2	1	1	2	1.00	2.00	2.00	1	1.00	2.00	2.00	1.00	1.00	1.00
18	208619	20	8.00	12.0	19.0	8.00	2002	2014.0	72	2	2	1	2	1	2	2	1	3	2	2	1	2	2	1	4	1	1	2	2	2	2	2	2	2	1	2	1.00	2.00	2.00	1	1.00	2.00	1.00	2.00	1.00	1.00
19	192361	27	25.00	2.0	10.0	204.00	2001	2003.0	36	2	1	1	2	2	3	2	2	1	2	2	4	1	2	1	4	1	1	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	1	1.00	2.00	1.00	2.00	1.00	4.00
20	211721	1	1.00	2.0	0.3	10.00	2003	2005.0	99	2	1	2	2	2	3	1	1	1	2	2	4	1	1	2	4	1	1	2	1	2	2	2	2	2	1	2	1.00	1.00	2.00	1	1.00	2.00	2.00	2.00	1.00	1.00
21	209350	33	25.00	8.0	13.0	240.00	2003	2011.0	48	2	1	2	2	2	2	3	1	1	2	2	2	1	2	2	4	1	1	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	1	1.00	2.00	2.00	2.00	1.00	4.00
22	213294	6	1.00	5.0	3.0	36.00	2004	2009.0	36	2	1	2	2	2	3	2	1	4	1	2	2	2	2	1	4	1	1	2	1	2	2	2	2	2	1	2	1.00	2.00	2.00	2	1.00	2.00	1.00	2.00	1.00	1.00
23	203627	45	41.00	4.0	14.0	360.00	2003	2007.0	99	2	1	2	2	2	2	2	2	1	2	2	1	2	2	2	4	1	2	2	2	2	1	2	2	2	1	1	2	1.00	1.00	2.00	2	2.00	1.00	1.00	2.00	1.00	5.00
24	200577	16	10.00	6.0	13.0	36.00	2003	2009.0	48	2	1	2	2	2	3	1	2	2	2	2	2	2	2	1	4	2	2	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	2	2.00	1.00	2.00	2.00	2.00	1.00
25	215455	13	9.00	4.0	1.5	144.00	2005	2009.0	60	2	1	2	2	2	2	1	1	1	1	2	4	1	2	1	3	1	1	2	2	2	2	2	2	1	1	2	2.00	1.00	2.00	2	1.00	2.00	2.00	1.00	1.00	3.00
26	208764	14	11.00	3.0	5.0	108.00	2003	2006.0	0	1	1	2	2	2	1	1	2	1	2	1	3	1	1	2	3	1	1	2	2	2	2	2	2	1	1	2	1.00	1.00	2.00	2	1.00	2.00	2.00	1.00	1.00	2.00
27	217559	8	6.00	2.0	2.5	72.00	2003	2005.0	99	1	1	2	2	2	3	2	1	3	2	2	1	1	2	1	2	1	1	2	2	1	1	1	1	1	4	2	2.00	2.00	1.00	2	1.00	2.00	1.00	1.00	1.00	2.00
28	220663	6	1.00	8.0	6.0	8.00	2003	2011.0	60	2	2	1	2	3	1	1	1	8	2	2	3	2	2	1	3	2	1	2	1	2	2	2	2	2	1	1	2	1.00	2.00	2.00	2	1.00	2.00	2.00	1.00	2.00	1.00
29	221161	6	0.10	6.0	5.0	12.00	2003	2009.0	48	2	1	2	2	2	3	1	2	2	2	2	4	2	2	2	4	1	1	2	2	2	2	2	2	2	1	2	1.00	2.00	2.00	2	1.00	2.00	2.00	1.00	1.00	1.00
30	229511	22	20.00	2.0	2.5	120.00	2004	2006.0	99	2	1	2	2	2	3	2	1	3	1	2	4	2	2	1	4	2	2	2	2	2	1	2	1	1	3	2	2.00	2.00	1.00	1	2.00	1.00	1.00	2.00	2.00	2.00
31	187413	21	13.00	8.0	8.0	136.00	2000	2008.0	99	1	1	2	2	2	3	3	1	2	1	2	2	2	1	2	3	2	2	2	2	2	1	2	2	2	1	1	2	1.00	2.00	2.00	1	2.00	1.00	2.00	1.00	2.00	3.00
32	228744	14	11.00	3.0	1.0	168.00	2005	2008.0	99	2	1	2	2	2	3	2	2	1	2	2	2	2	1	2	4	2	5	1	2	2	2	2	2	2	1	2	1.00	1.00	2.00	2	2.00	2.00	1.00	2.00	2.00	3.00
33	233770	33	32.00	1.0	32.0	6.00	2004	2005.0	99	2	1	2	2	2	1	2	1	1	2	2	3	2	2	2	3	1	1	2	2	2	2	2	2	2	1	2	2	2.00	1.00	2.00	1	1.00	2.00	1.00	1.00	1.00	1.00
34	230822	30	29.50	0.5	27.0	36.00	2005	2005.5	36	2	1	2	2	2	3	1	1	1	2	2	2	2	2	2	4	1	5	2	1	2	2	2	2	2	2	1	2	1.00	1.00	2.00	2	2.00	2.00	2.00	2.00	1.00	1.00
35	215194	26	22.00	4.0	10.0	192.00	2005	2009.0	48	2	1	2	2	2	2	2	2	1	1	2	3	1	2	1	4	1	1	2	2	2	2	1	2	2	2	1	2	1.00	1.00	2.00	2	1.00	2.00	1.00	2.00	1.00	4.00
36	192686	23	21.00	2.0	10.0	156.00	2005	2007.0	36	2	1	2	2	2	3	2	1	4	1	2	2	2	2	2	4	1	1	2	2	2	2	2	2	2	1	2	1.00	2.00	2.00	2	1.00	2.00	1.00	2.00	1.00	3.00
37	242079	11	8.00	3.0	1.5	120.00	2006	2009.0	35	2	1	2	2	2	1	1	2	1	2	2	4	1	1	1	4	1	1	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	1	1.00	2.00	2.00	2.00	1.00	2.00
38	253336	13	8.00	5.0	8.0	60.00	2006	2011.0	49	2	1	2	2	2	3	2	1	1	2	2	3	2	2	2	4	1	4	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	2	2.00	2.00	1.00	2.00	1.00	1.00
39	251837	1	0.10	2.0	15.0	288.00	2006	2008.0	56	1	1	2	2	2	2	1	2	1	2	2	2	2	1	1	4	1	5	2	2	2	1	1	1	1	2	2	2	2.00	1.00	2.00	2	2.00	2.00	2.00	2.00	1.00	5.00
40	241449	15	14.00	1.0	13.0	24.00	2007	2008.0	14	2	1	2	2	2	2	1	2	1	2	2	2	2	2	2	4	1	3	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	1	2.00	2.00	2.00	2.00	1.00	1.00
41	223504	24	23.00	1.0	21.0	36.00	2008	2009.0	14	2	1	2	2	1	3	2	2	1	1	2	4	2	1	1	4	1	1	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	1	1.00	2.00	1.00	2.00	1.00	1.00
42	256834	20	16.00	4.0	9.0	120.00	2005	2009.0	99	2	1	2	2	2	3	2	2	1	2	3	2	1	1	1	4	2	1	2	2	1	1	1	1	1	3	2	2.00	1.00	1.00	1	1.00	2.00	1.00	2.00	2.00	2.00
43	215601	23	14.00	9.0	19.0	36.00	2007	2016.0	84	2	1	2	2	1	1	2	1	2	2	2	2	2	2	2	4	2	1	2	2	2	2	2	2	2	1	2	1.00	2.00	2.00	1	1.00	2.00	1.00	2.00	2.00	1.00
44	257587	8	7.40	0.6	6.0	12.00	2007	2007.0	0	2	1	2	2	2	3	1	2	1	2	2	2	2	1	2	4	1	1	2	2	2	2	2	2	1	2	2	2	2.00	1.00	2.00	1	1.00	2.00	2.00	2.00	1.00	1.00
45	254483	15	10.00	5.0	14.0	10.00	2006	2011.0	49	2	1	2	2	2	1	2	2	1	1	2	1	2	2	1	4	1	1	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	1	1.00	2.00	1.00	2.00	1.00	1.00
46	257503	14	4.00	10.0	14.0	9.00	2006	2016.0	16	2	2	2	2	2	2	1	1	1	2	2	2	2	2	1	4	1	3	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	1	2.00	2.00	2.00	2.00	1.00	1.00
47	252438	18	12.00	6.0	12.0	72.00	2007	2013.0	62	2	1	2	2	2	3	1	1	9	1	1	2	2	2	1	4	1	5	2	2	2	2	2	2	2	1	1	2	1.00	2.00	2.00	2	2.00	2.00	2.00	2.00	1.00	2.00

Slno	hospital_number	Age	AgeSurgery	survival	age_at_onset_of_symptoms	duration_of_symptoms	dos	last_follow_up_date	AEDstoppedaftersxmonths	initial_precipitating_factors	seizures	FND	raised_ICP	others	seizures_frequency	TType	presence_of_aura	location_of_tumor	side	size	ct_density	calcification	associated_MTSHS	contrast_enhancement	surgery	post_excision_ECoG	HPR	wound_infection	FND_A	immediate_postop_seizure	@6month_seizure	@1_year	@1.5_year	last_follow_up_seizure	post_op_recurrance	engeloutcomescale	death	Excellentoutcome	IOCATION2	Outcome	Gender	Ganglio	Dnet	FocalwithGeneralisation	Subtotal	Nospikes	Durationsymptoms
48	239572	33	28.00	5.0	10.0	276.00	2006	2011.0	72	2	1	2	2	2	1	2	2	1	2	3	2	1	2	2	4	1	1	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	2	1.00	2.00	1.00	2.00	1.00	5.00
49	264458	12	11.00	1.0	5.0	84.00	2007	2008.0	0	2	1	2	2	2	3	2	2	1	1	1	2	2	2	1	4	2	1	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	1	1.00	2.00	1.00	2.00	2.00	2.00
50	256218	50	49.00	1.0	27.0	276.00	2007	2008.0	99	2	1	2	2	2	3	2	2	1	2	2	2	2	2	2	4	1	1	1	2	2	1	1	2	2	2	2	2.00	1.00	2.00	1	1.00	2.00	1.00	2.00	1.00	5.00
51	262305	9	4.00	5.0	6.0	36.00	2009	2014.0	38	2	1	2	2	2	3	1	1	4	2	1	2	2	2	2	4	3	2	2	2	2	2	2	2	2	1	2	1.00	2.00	2.00	1	2.00	1.00	2.00	2.00	2.00	1.00
52	267221	37	33.00	4.0	14.0	276.00	2007	2011.0	99	2	1	2	2	2	3	2	1	1	2	2	2	2	1	2	4	1	2	2	2	1	1	1	1	2	1	4	2	2.00	1.00	1.00	1	2.00	1.00	1.00	2.00	1.00	5.00
53	251065	19	17.00	2.0	5.0	168.00	2007	2009.0	32	2	1	2	2	2	3	1	1	1	1	3	2	2	2	2	4	1	2	2	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	2	2.00	1.00	2.00	2.00	1.00	3.00
54	273537	20	17.00	3.0	7.0	180.00	2008	2011.0	36	2	1	2	2	2	2	1	1	4	2	1	2	2	2	2	4	1	2	2	2	2	2	2	2	2	1	2	1.00	2.00	2.00	1	2.00	1.00	2.00	2.00	1.00	3.00
55	274862	25	19.00	6.0	23.0	12.00	2008	2014.0	99	2	1	2	2	2	3	2	2	1	1	2	3	2	2	2	4	1	2	1	2	2	2	2	1	1	2	3	2	2.00	1.00	1.00	1	2.00	1.00	1.00	2.00	1.00	1.00
56	280019	20	12.00	8.0	14.0	92.00	2008	2016.0	48	2	1	2	2	2	3	1	1	1	1	1	2	2	2	2	4	1	1	2	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	2	1.00	2.00	2.00	2.00	1.00	2.00
57	284002	33	29.00	4.0	16.0	192.00	2008	2012.0	99	2	1	1	2	2	3	2	1	3	1	2	2	2	2	2	4	1	5	2	2	2	1	1	2	2	2	3	2	2.00	2.00	1.00	1	2.00	2.00	1.00	2.00	1.00	4.00
58	244901	57	56.00	1.0	54.0	36.00	2008	2009.0	99	2	1	2	2	2	1	2	2	1	2	3	3	2	2	2	4	1	2	2	2	2	1	1	1	1	1	4	2	2.00	1.00	1.00	1	2.00	1.00	1.00	2.00	1.00	1.00
59	268888	25	20.00	5.0	25.0	1.00	2007	2012.0	62	2	1	2	2	1	1	3	2	2	1	2	2	2	2	1	4	1	1	2	2	1	2	2	2	2	2	1	2	1.00	2.00	2.00	1	1.00	2.00	2.00	2.00	1.00	1.00
60	269568	63	61.00	2.0	62.0	0.25	2007	2009.0	99	2	1	2	2	2	1	3	2	2	1	3	2	1	2	1	3	1	1	2	2	1	2	2	2	2	1	2	2	2.00	2.00	2.00	1	1.00	2.00	2.00	1.00	1.00	1.00
61	255942	14	12.00	2.0	6.0	98.00	2007	2009.0	36	2	1	2	2	2	2	1	2	2	1	2	2	1	2	1	4	1	1	2	2	1	2	2	2	2	2	1	2	1.00	2.00	2.00	2	1.00	2.00	2.00	2.00	1.00	2.00
62	271161	22	17.00	5.0	20.0	24.00	2007	2012.0	56	2	1	2	1	2	2	3	2	2	2	3	3	1	2	1	4	1	1	2	2	2	2	2	2	2	2	1	2	1.00	2.00	2.00	1	1.00	2.00	2.00	2.00	1.00	1.00
63	242544	15	12.00	3.0	1.0	180.00	2007	2010.0	36	2	1	2	2	2	2	1	1	1	2	2	2	1	2	1	4	1	1	2	2	2	1	2	2	2	2	1	2	1.00	1.00	2.00	1	1.00	2.00	2.00	2.00	1.00	3.00
64	271954	11	6.00	5.0	7.0	48.00	2011	2016.0	26	1	1	2	2	2	2	1	2	4	1	2	2	1	2	1	4	1	1	2	2	2	2	2	2	2	2	1	2	1.00	2.00	2.00	1	1.00	2.00	2.00	2.00	1.00	1.00
65	274341	33	29.00	4.0	15.0	216.00	2008	2012.0	99	2	1	2	2	2	3	2	1	1	1	2	2	2	1	2	4	1	1	2	2	2	2	2	1	1	2	3	2	2.00	1.00	1.00	1	1.00	2.00	1.00	2.00	1.00	4.00
66	267322	29	28.00	1.0	24.0	80.00	2008	2009.0	99	2	1	2	2	2	1	1	2	1	1	2	3	2	1	2	4	1	5	2	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	2	2.00	2.00	2.00	2.00	1.00	2.00
67	277207	20	13.00	7.0	16.0	48.00	2009	2016.0	34	1	1	2	2	2	1	1	1	1	1	1	2	2	2	1	4	1	1	2	2	1	2	2	2	2	2	1	2	1.00	1.00	2.00	1	1.00	2.00	2.00	2.00	1.00	1.00
68	222245	6	2.00	4.0	3.0	36.00	2004	2008.0	99	2	1	2	2	2	1	2	1	1	1	2	1	1	2	1	4	1	1	2	1	2	2	2	2	1	1	2	2	2.00	1.00	2.00	1	1.00	2.00	1.00	2.00	1.00	1.00
69	290972	18	13.00	5.0	13.0	72.00	2010	2015.0	28	2	1	2	2	2	3	1	1	1	1	1	2	2	2	1	4	1	1	2	2	1	2	2	2	2	2	1	2	1.00	1.00	2.00	2	1.00	2.00	2.00	2.00	1.00	2.00
70	296714	2	0.20	3.0	2.0	1.00	2009	2012.0	18	2	2	1	2	2	2	1	1	2	2	2	2	2	2	1	4	1	1	1	1	2	2	2	2	2	2	1	2	1.00	2.00	2.00	2	1.00	2.00	2.00	2.00	1.00	1.00
71	297148	17	12.00	5.0	17.0	6.00	2009	2014.0	30	2	2	1	2	1	3	1	1	10	2	1	3	2	2	1	3	1	1	1	1	2	2	2	2	2	2	1	2	1.00	2.00	2.00	1	1.00	2.00	2.00	1.00	1.00	1.00
72	282298	22	18.00	4.0	15.0	84.00	2009	2013.0	46	2	1	2	2	2	3	2	1	1	2	1	2	2	2	1	4	1	1	2	2	1	2	2	2	2	2	1	2	1.00	1.00	2.00	1	1.00	2.00	1.00	2.00	1.00	2.00
73	300472	37	36.00	1.0	33.0	148.00	2010	2011.0	99	2	1	2	2	2	2	2	2	1	2	2	2	1	2	1	4	1	1	2	2	2	1	2	2	1	2	3	2	2.00	1.00	1.00	1	1.00	2.00	1.00	2.00	1.00	3.00
74	304449	9	7.00	2.0	7.0	24.00	2010	2012.0	16	2	1	2	2	2	2	1	1	1	1	2	3	2	2	1	4	1	2	2	2	2	2	2	1	2	2	1	2	1.00	1.00	2.00	1	2.00	1.00	2.00	2.00	1.00	1.00
75	239636	19	18.00	1.0	12.0	84.00	2010	2011.0	14	2	1	2	2	2	3	2	1	1	2	2	1	1	2	1	4	1	1	2	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	1	1.00	2.00	1.00	2.00	1.00	2.00
76	296083	18	15.00	3.0	18.0	48.00	2011	2014.0	99	2	1	2	2	2	3	1	1	1	1	1	2	2	2	1	4	1	1	2	2	2	1	1	1	1	2	1	2	1.00	1.00	2.00	1	1.00	2.00	2.00	2.00	1.00	1.00
77	312148	16	11.00	5.0	16.0	2.00	2010	2015.0	99	2	1	2	2	2	2	1	1	1	1	2	1	2	2	1	4	1	2	2	2	2	2	2	2	1	1	2	2	2.00	1.00	2.00	1	2.00	1.00	2.00	2.00	1.00	1.00
78	315679	11	5.00	6.0	6.0	60.00	2012	2018.0	99	1	1	2	2	2	2	2	1	1	1	1	2	2	2	2	4	1	2	2	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	1	2.00	1.00	1.00	2.00	1.00	1.00
79	297114	9	1.00	8.0	2.0	84.00	2010	2018.0	24	2	1	2	2	2	3	1	1	1	1	1	1	2	2	2	4	1	1	2	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	1	1.00	2.00	2.00	2.00	1.00	2.00
80	303552	13	8.00	5.0	1.0	144.00	2011	2016.0	99	2	1	2	2	2	1	2	1	1	1	1	3	2	2	1	4	1	1	2	2	2	1	1	2	2	2	2	2	2.00	1.00	2.00	1	1.00	2.00	1.00	2.00	1.00	3.00
81	310429	54	51.00	3.0	53.0	6.00	2010	2013.0	0	2	1	2	2	2	2	1	1	1	1	3	2	2	2	2	4	1	1	2	2	2	2	2	2	1	1	2	1.00	1.00	2.00	1	1.00	2.00	2.00	2.00	1.00	1.00
82	312756	16	12.00	4.0	12.0	48.00	2012	2016.0	48	2	1	2	2	2	3	2	2	1	1	2	2	1	2	2	4	3	2	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	1	2.00	1.00	1.00	2.00	2.00	1.00
83	313656	18	14.00	4.0	18.0	1.00	2010	2014.0	49	2	2	1	2	1	2	1	1	1	1	3	2	1	2	1	4	1	1	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	1	1.00	2.00	2.00	2.00	1.00	1.00
84	322815	28	26.00	2.0	13.0	180.00	2014	2016.0	12	2	1	2	2	2	1	1	1	1	1	3	3	1	2	1	4	1	1	2	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	2	1.00	2.00	2.00	2.00	1.00	3.00
85	332180	32	26.00	6.0	12.0	240.00	2011	2017.0	99	1	1	2	2	2	3	2	1	1	1	2	3	1	2	1	4	1	2	2	2	2	2	2	1	1	2	3	2	2.00	1.00	1.00	2	2.00	1.00	1.00	2.00	1.00	4.00
86	333770	9	7.00	2.0	2.0	12.00	2012	2014.0	24	2	1	2	2	1	3	1	1	1	2	1	3	2	2	1	4	1	1	2	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	1	1.00	2.00	2.00	2.00	1.00	1.00
87	333782	1	0.20	3.0	1.0	8.00	2011	2014.0	20	2	2	2	2	1	2	2	2	7	2	2	3	2	2	1	4	3	1	1	2	2	2	2	2	2	1	2	1.00	2.00	2.00	1	1.00	2.00	1.00	2.00	2.00	1.00
88	334126	22	18.00	4.0	5.0	204.00	2012	2016.0	36	2	1	2	2	2	3	2	1	1	2	2	3	2	2	2	4	1	1	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	2	1.00	2.00	1.00	2.00	1.00	4.00
89	332308	18	17.00	1.0	18.0	2.00	2011	2012.0	22	2	1	2	2	2	2	1	2	1	1	1	3	2	2	1	4	1	1	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	1	1.00	2.00	2.00	2.00	1.00	1.00
90	319826	8	5.00	3.0	1.0	84.00	2012	2015.0	99	2	1	2	2	2	3	2	2	2	2	2	2	2	2	1	4	1	4	2	2	1	1	1	1	1	2	4	2	2.00	2.00	1.00	1	2.00	2.00	1.00	2.00	1.00	2.00
91	311044	35	30.00	5.0	24.0	132.00	2012	2017.0	36	2	1	2	2	2	3	1	1	1	1	3	3	2	2	1	4	1	2	2	2	2	1	2	2	2	2	1	2	1.00	1.00	2.00	2	2.00	1.00	2.00	2.00	1.00	3.00
92	325144	31	28.00	3.0	11.0	240.00	2014	2017.0	24	2	2	2	2	2	2	1	2	3	1	1	3	2	2	1	4	1	2	2	2	2	2	2	2	2	2	1	2	1.00	2.00	2.00	1	2.00	1.00	2.00	2.00	1.00	4.00
93	321346	14	10.00	4.0	6.0	84.00	2012	2016.0	64	1	1	2	2	2	3	1	1	1	2	1	2	2	2	1	4	2	2	2	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	2	2.00	2.00	2.00	2.00	1.00	2.00
94	323760	19	17.00	2.0	3.0	192.00	2011	2013.0	26	2	1	2	2	1	1	1	1	1	2	2	3	1	2	2	2	3	2	2	2	1	2	2	2	2	2	1	2	1.00	1.00	2.00	2	2.00	1.00	2.00	1.00	2.00	4.00

Slno	hospital_number	Age	AgeSurgery	survival	age_at_onset_of_symptoms	duration_of_symptoms	dos	last_follow_up_date	AEDstoppedaftersxmonths	initial_precipitating_factors	seizures	FND	raised_ICP	others	seizures_frequency	Type	presence_of_aura	location_of_tumor	side	size	ct_density	calcification	associated_MTSHS	contrast_enhancement	surgery	post_excision_ECoG	HPR	wound_infection	FND_A	immediate_postop_seizure	@6month_seizure	@1_year	@1.5_year	last_follow_up_seizure	post_op_recurrance	engeloutcomescale	death	Excellentoutcome	IOCATION2	Outcome	Gender	Ganglio	Dnet	FocalwithGeneralisation	Subtotal	Nospikes	Durationsymptoms
95	328045	12	9.00	3.0	6.0	72.00	2014	2017.0	99	2	1	2	2	1	1	1	1	3	1	1	3	2	2	2	4	3	2	2	2	2	1	1	1	1	2	4	2	2.00	2.00	1.00	2	2.00	1.00	2.00	2.00	2.00	2.00
96	281357	17	16.00	1.0	1.0	192.00	2013	2014.0	12	2	1	2	2	2	2	2	1	1	2	2	2	2	2	1	4	1	1	2	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	2	1.00	2.00	1.00	2.00	1.00	4.00
97	337211	9	7.00	2.0	6.0	36.00	2012	2014.0	24	1	1	2	2	2	3	1	2	3	2	2	2	2	2	2	4	1	2	2	2	2	2	2	2	2	2	1	2	1.00	2.00	2.00	1	2.00	1.00	2.00	2.00	1.00	1.00
98	321708	22	21.30	0.7	16.0	72.00	2016	2016.0	99	2	1	2	2	2	3	1	2	1	2	1	3	2	2	2	4	1	2	2	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	2	2.00	1.00	2.00	2.00	1.00	2.00
99	321073	13	12.60	0.4	3.0	120.00	2012	2012.0	24	2	1	2	2	2	1	1	1	1	2	1	3	2	2	1	4	1	2	2	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	1	2.00	1.00	2.00	2.00	1.00	2.00
100	343426	8	6.00	2.0	2.0	72.00	2012	2014.0	99	2	1	2	2	2	1	1	1	1	2	1	4	2	2	1	4	1	1	2	2	2	1	1	1	2	2	3	2	2.00	1.00	1.00	2	1.00	2.00	2.00	2.00	1.00	2.00
101	347160	13	9.00	4.0	3.0	120.00	2012	2016.0	24	2	1	2	2	2	3	1	1	1	1	2	2	1	2	1	4	1	2	2	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	2	2.00	1.00	2.00	2.00	1.00	2.00
102	347717	28	26.00	2.0	20.0	96.00	2012	2014.0	26	1	1	2	2	2	2	2	1	1	2	1	4	2	2	2	4	1	2	2	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	1	2.00	1.00	1.00	2.00	1.00	2.00
103	348564	9	5.00	4.0	6.0	36.00	2014	2018.0	99	2	1	2	2	2	3	1	2	1	1	1	2	2	2	2	4	1	2	2	2	2	1	2	2	2	2	3	2	2.00	1.00	1.00	1	2.00	1.00	2.00	2.00	1.00	1.00
104	350162	16	13.00	3.0	13.0	36.00	2013	2016.0	36	2	1	2	2	2	3	1	1	2	2	1	2	2	2	1	4	1	2	2	2	2	2	2	2	2	2	1	2	1.00	2.00	2.00	1	2.00	1.00	2.00	2.00	1.00	1.00
105	349105	13	9.00	4.0	9.0	48.00	2014	2018.0	24	2	1	2	2	2	2	1	2	1	2	1	2	2	2	1	4	1	1	2	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	1	1.00	2.00	2.00	2.00	1.00	1.00
106	333405	26	25.00	1.0	20.0	72.00	2014	2015.0	99	2	1	2	2	2	1	2	2	1	2	1	3	2	2	2	4	1	1	2	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	1	1.00	2.00	1.00	2.00	1.00	2.00
107	352092	22	20.00	2.0	8.0	134.00	2013	2015.0	36	2	1	2	2	2	3	2	2	1	1	1	2	2	2	1	4	1	2	2	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	2	2.00	1.00	1.00	2.00	1.00	3.00
108	344483	31	26.00	5.0	8.0	264.00	2012	2017.0	72	2	1	2	2	2	2	2	2	1	2	1	2	3	1	2	1	3	2	2	2	2	1	1	2	2	2	1	3	2	2.00	2.00	1.00	1	2.00	1.00	1.00	1.00	2.00	5.00
109	300541	13	8.00	5.0	3.0	120.00	2011	2016.0	24	1	1	2	2	2	1	1	1	1	2	1	2	2	1	2	4	2	2	2	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	1	2.00	1.00	2.00	2.00	2.00	2.00
110	296221	6	3.00	3.0	4.0	24.00	2009	2012.0	92	2	1	2	2	2	3	2	1	1	1	1	2	2	2	2	4	1	1	2	2	2	1	1	1	2	1	3	2	2.00	1.00	1.00	1	1.00	2.00	1.00	2.00	1.00	1.00
111	339193	34	32.00	2.0	19.0	180.00	2013	2015.0	24	2	1	2	2	2	2	1	2	1	1	1	2	2	2	2	4	1	1	2	2	2	1	2	2	2	2	1	2	1.00	1.00	2.00	1	1.00	2.00	2.00	2.00	1.00	3.00
112	357436	19	18.00	1.0	10.0	108.00	2013	2014.0	99	2	1	1	2	2	3	2	2	1	2	2	3	2	2	1	3	2	1	2	2	2	1	2	1	1	1	3	2	2.00	1.00	1.00	1	1.00	2.00	1.00	1.00	2.00	2.00
113	289171	10	7.00	3.0	5.0	60.00	2013	2016.0	15	2	1	2	2	2	2	2	1	1	4	1	2	3	1	2	1	4	1	1	2	2	2	2	2	2	2	1	2	1.00	2.00	2.00	1	1.00	2.00	2.00	2.00	1.00	1.00
114	363044	18	16.00	2.0	15.0	36.00	2013	2015.0	24	2	1	2	2	2	3	1	1	1	1	1	2	1	2	1	4	1	1	2	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	1	1.00	2.00	2.00	2.00	1.00	1.00
115	369201	31	30.00	1.0	18.0	16.00	2014	2015.0	26	2	1	2	2	2	1	1	1	1	1	1	2	2	2	2	4	1	1	2	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	1	1.00	2.00	2.00	2.00	1.00	1.00
116	356500	4	1.00	3.0	1.0	36.00	2013	2016.0	24	2	1	2	2	2	3	1	2	3	1	1	3	2	2	2	4	1	2	2	2	2	2	2	2	2	2	1	2	1.00	2.00	2.00	1	2.00	1.00	2.00	2.00	1.00	1.00
117	344419	23	22.80	0.2	17.0	272.00	2013	2013.0	99	2	1	2	2	2	1	2	2	1	1	1	1	1	2	2	4	1	2	2	2	1	1	2	1	1	2	4	2	2.00	1.00	1.00	1	2.00	1.00	1.00	2.00	1.00	5.00
118	360178	11	8.00	3.0	6.0	60.00	2014	2017.0	36	2	1	2	2	2	1	1	1	1	2	1	2	1	2	2	4	1	1	2	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	2	1.00	2.00	2.00	2.00	1.00	1.00
119	358962	3	0.10	3.0	1.0	24.00	2013	2016.0	24	2	1	2	2	2	1	1	1	1	1	3	3	2	2	2	4	1	2	2	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	1	2.00	1.00	2.00	2.00	1.00	1.00
120	339532	18	16.00	2.0	12.0	72.00	2014	2016.0	99	2	1	2	2	2	3	1	1	1	1	2	2	2	2	2	4	1	2	2	1	2	2	2	2	1	2	3	2	2.00	1.00	1.00	1	2.00	1.00	2.00	2.00	1.00	2.00
121	356499	23	21.00	2.0	17.0	60.00	2014	2016.0	24	2	1	2	2	2	2	2	2	1	1	1	2	2	2	2	4	1	2	2	2	2	2	2	1	2	2	1	2	1.00	1.00	2.00	1	2.00	1.00	1.00	2.00	1.00	1.00
122	281357	17	14.00	3.0	1.0	192.00	2013	2016.0	20	2	1	2	2	2	3	2	1	3	1	2	2	2	2	1	4	2	2	2	1	2	1	2	2	2	2	1	2	1.00	2.00	2.00	2	2.00	1.00	1.00	2.00	2.00	4.00
123	359378	6	2.00	4.0	5.0	15.00	2013	2017.0	26	2	1	2	2	2	1	1	1	2	2	2	2	2	2	2	4	1	2	2	2	2	2	2	2	2	2	1	2	1.00	2.00	2.00	1	2.00	1.00	2.00	2.00	1.00	1.00
124	364985	15	13.00	2.0	1.0	180.00	2014	2016.0	99	2	1	2	2	2	1	2	1	11	1	2	3	1	1	1	4	1	1	2	2	2	1	2	2	2	2	2	2	2.00	2.00	2.00	1	1.00	2.00	1.00	2.00	1.00	3.00
125	296761	21	18.00	3.0	4.0	204.00	2013	2016.0	99	2	1	2	2	2	2	3	2	1	2	2	3	2	2	2	3	2	2	2	2	2	1	1	1	1	1	3	2	2.00	1.00	1.00	1	2.00	1.00	2.00	1.00	2.00	4.00
126	367134	13	10.00	3.0	10.0	36.00	2014	2017.0	36	2	1	2	2	1	3	1	2	3	1	2	2	2	2	2	4	1	2	2	2	1	2	2	2	2	2	1	2	1.00	2.00	2.00	1	2.00	1.00	2.00	2.00	1.00	1.00
127	261317	19	16.00	3.0	2.0	192.00	2013	2016.0	26	2	1	2	2	2	3	2	1	11	2	2	2	1	1	1	4	1	1	2	2	1	2	2	2	2	2	1	2	1.00	2.00	2.00	1	1.00	2.00	1.00	2.00	1.00	4.00
128	366077	21	19.00	2.0	17.0	48.00	2014	2016.0	26	2	1	2	2	2	1	3	2	2	2	1	4	1	2	1	4	2	1	2	2	1	2	2	2	2	2	1	2	1.00	2.00	2.00	1	1.00	2.00	2.00	2.00	2.00	1.00
129	322613	8	6.00	2.0	1.0	84.00	2014	2016.0	99	2	1	2	2	2	3	2	1	11	1	1	2	2	1	1	3	2	3	2	2	2	1	1	1	1	1	3	2	2.00	2.00	1.00	2	2.00	2.00	1.00	1.00	2.00	2.00
130	377291	32	31.00	1.0	27.0	36.00	2015	2016.0	24	2	1	2	2	2	1	3	2	11	2	1	2	2	1	2	4	1	2	2	2	2	2	1	1	1	2	3	2	2.00	2.00	1.00	1	2.00	1.00	2.00	2.00	1.00	1.00
131	380905	9	6.00	3.0	5.0	48.00	2014	2017.0	99	2	1	2	2	2	3	1	2	1	2	3	3	1	2	1	4	1	2	2	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	2	2.00	1.00	2.00	2.00	1.00	1.00
132	382421	2	0.10	2.0	1.0	12.00	2014	2016.0	24	2	2	2	2	1	3	2	2	2	2	3	2	2	2	1	4	1	1	2	2	1	2	2	2	2	2	1	2	1.00	2.00	2.00	2	1.00	2.00	1.00	2.00	1.00	1.00
133	381330	33	31.00	2.0	32.0	12.00	2014	2016.0	99	2	2	2	2	1	2	1	1	4	2	2	2	2	2	1	3	2	1	2	2	2	2	2	1	2	2	2	2	2.00	2.00	2.00	2	1.00	2.00	2.00	1.00	2.00	1.00
134	373915	8	4.00	4.0	6.0	24.00	2014	2018.0	48	2	1	2	2	2	3	1	1	1	1	2	2	2	2	2	4	1	1	2	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	2	1.00	2.00	2.00	2.00	1.00	1.00
135	383294	24	23.00	1.0	21.0	36.00	2015	2016.0	36	2	1	2	2	2	3	1	1	1	2	1	2	2	2	1	4	1	3	2	2	1	2	2	2	2	2	1	2	1.00	1.00	2.00	2	2.00	2.00	2.00	2.00	1.00	1.00
136	385892	24	22.00	2.0	12.0	144.00	2015	2017.0	34	2	1	2	2	2	2	2	1	1	1	2	2	1	2	1	4	1	1	2	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	2	1.00	2.00	1.00	2.00	1.00	3.00
137	388182	27	25.00	2.0	23.0	48.00	2015	2017.0	99	2	1	2	2	3	1	1	2	11	1	2	2	1	2	1	4	1	5	2	2	2	2	2	2	2	2	1	2	1.00	2.00	2.00	1	2.00	2.00	2.00	2.00	1.00	1.00
138	378495	16	14.00	2.0	8.0	96.00	2015	2017.0	99	2	1	2	2	2	2	2	2	1	2	2	3	1	2	2	4	1	1	2	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	2	1.00	2.00	1.00	2.00	1.00	2.00
139	315876	7	5.00	2.0	3.0	48.00	2015	2017.0	16	2	1	2	2	2	1	2	1	2	1	2	2	2	2	2	4	1	2	2	2	2	2	2	2	2	2	1	2	1.00	2.00	2.00	2	2.00	1.00	1.00	2.00	1.00	1.00
140	383544	15	14.00	1.0	10.0	60.00	2015	2016.0	14	2	1	2	2	2	3	1	1	11	1	3	2	2	2	2	4	2	2	2	2	2	2	2	2	2	2	1	2	1.00	2.00	2.00	2	2.00	1.00	2.00	2.00	2.00	1.00
141	341762	21	20.70	0.3	6.0	192.00	2015	2015.0	99	2	1	2	2	2	2	2	2	6	2	2	2	1	1	2	4	1	1	2	2	1	1	1	2	2	1	4	2	2.00	2.00	1.00	2	1.00	2.00	1.00	2.00	1.00	4.00

Slno	hospital_number	Age	AgeSurgery	survival	age_at_onset_of_symptoms	duration_of_symptoms	dos	last_follow_up_date	AEDstoppedaftersxmonths	initial_precipitating_factors	seizures	FND	raised_ICP	others	seizures_frequency	Type	presence_of_aura	location_of_tumor	side	size	ct_density	calcification	associated_MTSHS	contrast_enhancement	surgery	post_excision_ECoG	HPR	wound_infection	FND_A	immediate_postop_seizure	@6month_seizure	@1_year	@1.5_year	last_follow_up_seizure	post_op_recurrance	engeloutcomescale	death	Excellentoutcome	IOCATION2	Outcome	Gender	Ganglio	Dnet	FocalwithGeneralisation	Subtotal	Nospikes	Durationsymptoms
142	386399	12	9.00	3.0	6.0	72.00	2015	2018.0	36	2	1	2	2	1	3	1	2	2	1	1	3	1	2	2	4	1	1	2	2	2	2	2	2	2	1	2	1.00	2.00	2.00	2	1.00	2.00	2.00	2.00	1.00	2.00
143	370220	5	3.00	2.0	3.0	24.00	2015	2017.0	24	2	1	2	2	2	2	3	2	3	1	2	3	2	2	1	4	1	1	2	2	2	2	2	2	2	1	2	1.00	2.00	2.00	2	1.00	2.00	2.00	2.00	1.00	1.00
144	399223	3	1.00	2.0	2.0	12.00	2015	2017.0	25	2	1	2	2	2	2	2	2	5	2	1	2	2	2	2	4	1	1	2	1	2	2	2	2	2	1	2	1.00	2.00	2.00	1	1.00	2.00	1.00	2.00	1.00	1.00
145	398877	8	6.00	2.0	6.0	24.00	2016	2018.0	20	2	1	2	2	2	1	2	2	2	1	2	2	1	2	1	4	1	1	2	2	2	2	2	2	2	1	2	1.00	2.00	2.00	1	1.00	2.00	1.00	2.00	1.00	1.00
146	391043	42	40.00	2.0	8.0	96.00	2015	2017.0	24	2	1	1	2	2	1	2	1	6	1	1	2	2	1	2	4	1	2	2	2	2	2	2	2	1	2	2	2.00	2.00	2.00	1	2.00	1.00	1.00	2.00	1.00	2.00
147	377067	26	25.00	1.0	13.0	156.00	2016	2017.0	24	2	1	2	2	2	1	1	1	2	1	2	3	1	2	1	4	1	1	2	1	2	2	2	2	2	1	2	1.00	2.00	2.00	1	1.00	2.00	2.00	2.00	1.00	3.00
148	383978	17	16.00	1.0	14.0	36.00	2016	2017.0	99	2	1	2	2	2	3	1	2	1	1	2	2	1	2	1	4	1	2	2	2	2	2	2	1	1	2	3	2	2.00	1.00	1.00	1	2.00	1.00	2.00	2.00	1.00	1.00
149	320285	7	1.00	12.0	2.0	60.00	2005	2017.0	99	2	1	2	2	2	1	1	1	1	1	1	3	1	1	1	4	2	1	2	2	2	2	2	1	2	1	2	2	2.00	1.00	2.00	1	1.00	2.00	2.00	2.00	2.00	1.00
150	372936	22	21.30	0.7	10.0	144.00	2016	2016.0	99	2	1	2	2	2	3	1	1	1	2	2	2	1	1	1	4	1	3	2	2	2	1	2	1	1	1	3	2	2.00	1.00	1.00	1	2.00	2.00	2.00	2.00	1.00	3.00
151	392680	9	7.00	2.0	2.0	84.00	2016	2018.0	12	2	1	2	2	2	1	1	1	11	1	1	3	1	2	1	4	1	4	2	2	2	2	2	2	2	1	2	1.00	2.00	2.00	1	2.00	2.00	2.00	2.00	1.00	2.00
152	388309	11	9.00	2.0	3.0	96.00	2016	2018.0	24	2	1	2	2	2	3	1	1	6	1	2	3	2	2	2	4	1	2	2	2	2	2	2	2	2	1	2	1.00	2.00	2.00	2	2.00	1.00	2.00	2.00	1.00	2.00
153	299941	24	23.20	0.8	16.0	96.00	2016	2016.0	14	2	1	2	2	2	1	3	2	2	1	1	2	2	2	2	4	1	2	2	2	2	2	2	2	2	1	2	1.00	2.00	2.00	1	2.00	1.00	2.00	2.00	1.00	2.00
154	423605	18	17.00	1.0	12.0	72.00	2016	2017.0	24	2	2	1	2	4	3	1	2	8	2	3	2	2	2	1	2	1	1	2	2	2	2	2	2	2	1	2	1.00	2.00	2.00	2	1.00	2.00	2.00	1.00	1.00	2.00
155	373691	24	23.00	1.0	13.0	132.00	2015	2016.0	20	2	1	2	2	2	2	2	2	1	2	3	2	1	2	1	4	1	2	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	1	2.00	1.00	1.00	2.00	1.00	3.00
156	365994	18	15.00	3.0	14.0	48.00	2014	2017.0	36	2	1	2	2	2	3	1	1	1	2	2	3	1	2	1	4	1	5	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	2	2.00	2.00	2.00	2.00	1.00	1.00
157	381803	7	5.00	2.0	2.0	60.00	2015	2017.0	23	2	1	2	2	2	3	1	1	1	1	1	2	2	2	1	4	1	1	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	1	1.00	2.00	2.00	2.00	1.00	1.00
158	372867	3	1.00	2.0	1.0	224.00	2014	2016.0	99	2	1	2	2	2	3	1	2	2	2	2	3	2	2	1	3	2	2	2	2	2	1	1	1	1	1	3	2	2.00	2.00	1.00	1	2.00	1.00	2.00	1.00	2.00	4.00
159	382175	18	16.00	2.0	8.0	120.00	2014	2016.0	22	2	1	2	2	2	3	2	2	2	2	1	2	2	2	2	4	2	3	2	2	2	2	2	2	2	1	2	1.00	2.00	2.00	2	2.00	2.00	1.00	2.00	2.00	2.00
160	361272	17	15.00	2.0	4.0	156.00	2015	2017.0	26	2	1	2	2	2	3	1	2	11	2	2	3	2	1	1	4	1	1	2	2	2	2	2	2	2	1	2	1.00	2.00	2.00	2	1.00	2.00	2.00	2.00	1.00	3.00
161	386077	25	23.00	2.0	10.0	170.00	2015	2017.0	24	2	1	2	2	2	3	2	1	1	1	1	2	2	2	2	4	1	1	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	1	1.00	2.00	1.00	2.00	1.00	3.00
162	390821	34	31.00	3.0	33.0	10.00	2015	2018.0	99	2	1	2	2	2	3	1	1	11	1	3	3	2	2	1	3	2	2	2	2	2	2	2	2	1	1	2	1.00	2.00	2.00	2	2.00	1.00	2.00	1.00	2.00	1.00
163	391895	45	43.00	2.0	3.0	516.00	2016	2018.0	20	2	1	2	2	1	1	1	2	11	2	1	2	2	2	1	4	1	1	2	2	2	2	2	2	2	1	2	1.00	2.00	2.00	1	1.00	2.00	2.00	2.00	1.00	5.00
164	393045	17	16.00	1.0	13.0	48.00	2016	2017.0	99	2	1	2	2	2	2	1	1	1	1	2	2	2	2	2	4	2	2	2	2	2	1	2	1	1	2	3	2	2.00	1.00	1.00	1	2.00	1.00	2.00	2.00	2.00	1.00
165	384253	17	13.00	4.0	16.0	12.00	2014	2018.0	38	2	1	2	2	2	1	2	2	11	2	1	1	2	2	2	4	1	2	2	2	2	2	2	2	2	1	2	1.00	2.00	2.00	2	2.00	1.00	1.00	2.00	1.00	1.00
166	367561	12	10.00	2.0	10.0	24.00	2015	2017.0	99	2	1	2	2	2	3	1	1	1	1	1	2	2	2	1	4	1	2	2	2	1	2	2	1	2	2	2	2	2.00	1.00	2.00	1	2.00	1.00	2.00	2.00	1.00	1.00
167	385090	16	14.00	2.0	6.0	120.00	2016	2018.0	22	2	1	2	2	2	1	1	1	6	2	1	3	2	1	1	4	1	2	2	2	2	2	2	2	2	1	2	1.00	2.00	2.00	1	2.00	1.00	2.00	2.00	1.00	2.00
168	401032	8	7.00	1.0	4.0	48.00	2016	2017.0	26	2	1	2	2	2	2	1	1	3	1	3	3	2	2	2	4	1	2	2	2	2	2	2	2	2	1	2	1.00	2.00	2.00	2	2.00	1.00	2.00	2.00	1.00	1.00
169	375120	10	9.00	1.0	3.0	84.00	2016	2017.0	99	2	1	2	2	2	3	1	1	6	1	1	2	2	2	1	4	1	1	2	2	2	2	2	2	2	1	2	1.00	2.00	2.00	2	1.00	2.00	2.00	2.00	1.00	2.00
170	365847	13	12.00	1.0	8.0	60.00	2016	2017.0	99	2	1	2	2	2	1	1	1	3	2	1	3	2	2	2	4	1	2	2	2	2	1	1	2	2	2	2	2	2.00	2.00	2.00	2	2.00	1.00	2.00	2.00	1.00	1.00
171	403755	15	14.00	1.0	10.0	60.00	2017	2018.0	99	2	1	2	2	2	2	2	1	6	2	2	2	2	1	2	4	1	1	2	2	2	2	2	2	2	1	2	1.00	2.00	2.00	1	1.00	2.00	1.00	2.00	1.00	1.00
172	405460	12	11.00	1.0	8.0	48.00	2016	2017.0	99	1	1	2	2	2	1	1	1	3	1	2	2	2	2	2	4	1	2	2	2	2	2	2	2	2	1	2	1.00	2.00	2.00	2	2.00	1.00	2.00	2.00	1.00	1.00
173	406137	12	10.00	2.0	8.0	48.00	2016	2018.0	99	2	1	2	2	2	2	3	2	2	1	2	3	2	2	2	3	2	2	2	2	2	2	2	2	2	1	2	1.00	2.00	2.00	2	2.00	1.00	2.00	1.00	2.00	1.00
174	407221	12	11.00	1.0	10.0	24.00	2016	2017.0	12	2	1	2	2	2	3	1	1	1	1	1	2	1	1	1	4	1	1	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	2	1.00	2.00	2.00	2.00	1.00	1.00
175	410826	35	34.00	1.0	13.0	264.00	2016	2017.0	14	2	1	2	2	2	2	1	1	1	1	1	2	2	2	2	4	1	1	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	2	1.00	2.00	2.00	2.00	1.00	5.00
176	382625	9	7.00	2.0	7.0	24.00	2016	2018.0	12	2	1	2	2	2	3	1	1	1	1	1	2	1	1	2	4	2	2	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	2	2.00	1.00	2.00	2.00	2.00	1.00
177	409838	14	13.00	1.0	8.0	96.00	2016	2017.0	99	2	1	2	2	2	2	2	1	1	2	3	2	1	2	1	4	1	2	2	2	2	1	1	1	2	3	2	2.00	1.00	1.00	1	2.00	1.00	1.00	2.00	1.00	2.00
178	407779	29	28.00	1.0	2.0	24.00	2016	2017.0	99	1	1	2	2	2	3	1	2	7	2	1	2	1	2	1	4	1	1	2	2	2	2	2	2	2	1	2	1.00	2.00	2.00	1	1.00	2.00	2.00	2.00	1.00	1.00
179	330497	43	42.00	1.0	35.0	96.00	2017	2018.0	99	2	1	2	2	2	3	2	1	1	1	1	3	2	2	1	4	1	2	2	2	2	2	2	2	2	1	2	1.00	1.00	2.00	2	2.00	1.00	1.00	2.00	1.00	2.00

POST SURGICAL OUTCOME OF LONG TERM EPILEPSY ASSOCIATED TUMORS (LEAT): A RETROSPECTIVE COHORT STUDY

THESIS

SUBMITTED IN PARTIAL FULFILLMENT FOR DEGREE OF

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CERTIFICATE

This is to certify that the work incorporated in this thesis titled

"POST SURGICAL OUTCOME OF LONG TERM EPILEPSY ASSOCIATED TUMORS (LEAT): A RETROSPECTIVE COHART STUDY"

for the degree of

M.Ch NEUROSURGERY

has been carried out by DR. PRADEEPANAND VAIDYA

under my supervision and guidance. The work done in connection with this thesis has been carried out by the candidate himself and is genuine.

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DECLARATION

This thesis titled **"Post Surgical Outcome of Long Term Epilepsy Associated Tumors (LEAT): A Retrospective Cohort Study"** is a consolidated report based on a bonafide study of the period from January 1998 to December 2016, done by me under the Department of Neurosurgery, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram.

This thesis is submitted to SCTIMST in partial fulfillment of rules and regulations of M.Ch Neurosurgery examination.

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