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Surgery for drug-resistant tuberous sclerosis complex-associated epilepsy: who, when, and what

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ABSTRACT

Objective. Tuberous sclerosis complex (TSC) is a multisystem genetic disorder associated with refractory early-onset epilepsy. Current evidence supports surgery as the intervention most likely to achieve long-term seizure freedom, but no specific guidelines are available on TSC pre-surgical workup. This critical review assesses which TSC patients are suitable for surgical treatment, when pre-surgical evaluation should start, and what degree of surgical resection is optimal for postsurgical outcome.

Methods. We searched for publications from 2000 to 2020 in Pubmed and Embase using the terms "tuberous sclerosis," "epilepsy," and "epilepsy surgery". To evaluate postsurgical seizure outcome, we selected only studies with at least one year of follow-up.

Results. Overall, we collected data on 1,026 patients from 34 studies. Age at surgery ranged from one month to 54 years. Mean age at surgery was 8.41 years. Of the diagnostic non-invasive pre-surgical tools, MRI and video-EEG were considered most appropriate. Promising data for epileptogenic tuber detection is provided from invasive SEEG studies. Data on surgery and related outcome were available for 769 patients. Seizure freedom was seen in 64.4% of patients who underwent tuberectomy, 68.9% treated with lobectomy and 65.1% with multilobar resection. The most effective surgical approach was lobectomy, even though more recently tuberectomy associated with the resection of the peritubeal area seems to be the best approach to reach seizure freedom. Published postsurgical seizure freedom rates in patients with TSC were between 65% and 75%, but reduced to 48%-57% over longer follow-up periods. Early surgery might positively affect neurodevelopmental trajectory in some patients, even though data on cognitive outcome are still to be confirmed with longitudinal studies.

Significance. Considering the strong correlation between epilepsy duration and neurocognitive outcome, all patients with TSC ought to be referred early to a dedicated epilepsy centre for individually tailored pre-surgical evaluation by a multidisciplinary epilepsy surgery team.

Key words: TSC; epilepsy surgery; drug-resistant epilepsy; outcome; infantile spasms

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Tuberous sclerosis complex (TSC) is a multisystem, autosomal dominant, neurocutaneous syndrome with an incidence of 1 in 6,000-22,000 live births [1, 2].

Approximately 85% of these patients carry the pathogenic variants of the *TSC1* or *TSC2* genes, which are responsible for suppression of inhibition of the 'mammalian target of rapamycin' (mTOR), producing the cardinal excessive activation of the mTOR signalling pathway [3]. This complex pathway controls several cellular functions, including cell growth and differentiation, metabolism and autophagy [4, 5]. mTOR pathway mutations seem to focus on mTOR complex 1 (mTOR and raptor, its binding partner; mTORC1) as a common signalling node.

Aberrant mTOR-signalling in TSC results in hamartomas, neuropsychiatric disorders and epilepsy [3]. Consequently, patients with TSC display a large spectrum of neuropsychiatric symptoms, including epileptic seizures, intellectual disability, behavioural abnormalities, and autism spectrum disorder (ASD) [6] . Epilepsy is the most common of the neurological manifestations, occurring in 80-90% of patients with TSC [7]. Patients with TSC may experience several seizure types: focal and generalized motor seizures, epileptic spasms (ES), tonic, atonic, or tonic-clonic seizures. Two thirds of patients have drug-resistant epilepsy [8]. However, first seizures can be subtle and, therefore, may be unrecognized by parents [6]. Onset of seizures during the first year of life is seen in 62.5-73% of patients with TSC [8]. The most common seizure type in patients with TSC during this first year is ES, and 75% of these patients become drug resistant; even in patients without a history of ES, 40% develop drug-resistant epilepsy [8].

Patients with TSC are also at high risk of neurodevelopmental disorders, reported as tuberous sclerosis-associated neuropsychiatric disorders (TAND) [9] which are strongly related to early onset of seizures and drug resistance [10]. In this context, patients with early-onset ES experience a higher degree of intellectual disability than patients experiencing either late-onset ES or other seizures types [11, 12].

Despite the introduction of targeted drugs for TSC, such as vigabatrin and mTOR inhibitors, we are still not able to predict who are the patients that will benefit from these treatments, and more than half of patients still present with seizures [13, 14].

Surgery is a currently under-utilized but an important treatment option for patients with refractory TSC-associated epilepsy [15]. Of 1,852 patients with epilepsy in the international 'TuberOus SClerosis registry to increase disease Awareness' (TOSCA) registry, surgery (resective or palliative) was performed in 10.7% of patients with focal seizures and in 6.4% of patients with infantile spasms [16]. In comparison, mTOR inhibitors were prescribed in 7.7% of patients with focal seizures and 5.5% of patients with infantile spasms.

Epilepsy surgery planning in TSC faces major challenges, mainly related to the presence of multiple lesions (tubers) [17]. Considering the target of pre-surgical evaluation, it was debated whether, in the epileptogenic network, the "epileptogenic tuber" is associated with the surrounding altered cortex or not. Accurate localization of the complex epileptogenic network should be tailored to the individual patient, as the presence of multiple tubers is a limitation in standard procedures. Considering these difficulties, approaches have varied between different centres, depending on the focus on clinical, scalp, or invasive EEG, and on functional neuroimaging [17]. Current recommendations suggest identifying the target tuber with a view to avoiding multifocal and even bilateral resection [6]. However, how this goal should be achieved is still debated and no clear agreement exists regarding the most suitable TSC patients and which diagnostic tools should be preferred. Optimal surgical approaches remain to be identified and some form of multistage surgery is still performed [18].

In face of this problematic approach, published meta-analyses from 2013 [19, 20] support that surgery is successful for the majority of patients with TSC, rendering them seizure-free, with a seizure freedom rate of 56% at two years of follow-up [19], and 59% at one year [20]. Since the publication of these metanalyses, the 2018 International TSC consensus conference [6] suggested that: "…early pre-surgical evaluation should be immediately recommended after drug resistance is proved, and multifocal and bilateral lesions do not preclude pre-surgical assessment".

Many predictive factors of seizure freedom have been evaluated, ranging from clinical and neurophysiological features to genetic findings [19-21].

The amount and localization of cortical tubers might play a crucial role in neurocognitive outcome in TSC patients, as tubers result from a disruption in neuronal migration and white matter maturational processes.

It is widely known that a higher number of cortical tubers seem to be correlated to poorer cognitive outcome [10, 22]. A meta-analysis by Goodman [23] suggested that the cortical tuber count might be a biomarker for the severity of mental impairment and cerebral dysfunction in TSC patients. More recently, some authors suggested that tuber burden, rather than total number of tubers, might be a better predictor of seizure and IQ [24].

Some studies also considered whether the tuber location might influence cognitive and developmental outcome; a negative correlation between right frontal and parietal tuber location and IQ scores has been reported [25, 26]. Also, a negative correlation with posterior tuber localization and cognitive outcome has been described [27].

It is clear that intellectual disability is very common in TSC patients, and might be related to genetic variants (*TSC1* or *TSC2* mutations) as well as epileptic history [28].

TSC2 genetic variants are well known to be the most frequent variants and cause a more severe phenotype relative to *TSC1* variants. TSC2 patients have an earlier age at seizure onset, a lower level of cognitive abilities, and a greater tuber load than those with *TSC1* variants [29]. Few papers have looked specifically at correlations between seizure outcome and genotype, though TSC2 patients seem to have slightly worse outcomes [30, 31], even if these results have not always been universally supported [32]. A definitive answer on the correlation between postsurgical seizure outcome and genotype remains to be clarified based on the existing data.

Despite these efforts, firm conclusions cannot be drawn due to the fact that most of the studies are retrospective or specific to the experience of a single centre.

We performed a critical review of the current literature regarding pre and post-surgical evaluation in patients with TSC in order to analyse which diagnostic tools were used and their relationship with postsurgical outcome. Moreover, we have tried to determine from this who are the most suitable candidates, when surgery should be performed, and what should be removed during surgery.

Methods

Two authors (CP and NS) performed a search of PubMed and EMBASE databases using the following search strategy: "tuberous sclerosis", "epilepsy" and "epilepsy surgery" in different combinations ("tuberous sclerosis"[MeSH Terms] OR ("tuberous"[All Fields] AND "sclerosis"[All Fields]) OR "tuberous sclerosis"[All Fields]) AND (("epilepsy"[MeSH Terms] OR "epilepsy"[All Fields]) AND ("surgery"[Subheading] OR "surgery"[All Fields] OR "surgical procedures, operative"[MeSH Terms] OR ("surgical"[All Fields] AND "procedures"[All Fields] AND "operative"[All Fields]) OR "operative surgical procedures"[All Fields] OR "surgery"[All Fields].

Two authors independently screened all titles and abstracts of studies identified by the initial search. Studies were initially included if they:

- involved individuals with TSC-associated epilepsy who underwent surgical treatment;
- reported data concerning postsurgical epilepsy outcome and pre-surgical assessment;
- were written in English;
- were published within 20 years of the search date (January 2000–May 2020), which was considered a sufficient period to capture publications with the most reliable and appropriate diagnostic and surgical procedures.

The full text of an article was obtained when inclusion criteria were fulfilled according to either reviewer. We included in this article both reviews and metanalysis, however only data from original articles were considered for the results section. Upon uncertainty for inclusion of a publication, an additional author was consulted (LDP).

The aim of this review was to evaluate and discuss possible factors predictive of seizure freedom following surgery based on the published literature. We have structured our review according to the following topics.

Clinical and genetics findings:

- epilepsy phenotype and neuropsychiatric background;
- *TSC1* and *TSC2* mutations.

The different non-invasive and invasive diagnostic tools that have been used in patients with TSC to delineate the epileptogenic zone (EZ):

- non-invasive recordings: video-EEG and source localization procedures;
- structural neuroimaging: brain MRI and DTI;
- EEG-MRI concordance;
- functional neuroimaging: PET and SPECT;
- invasive recordings: SEEG and subdural grids;
- histopathological results.

Type of surgery:

- resective *vs* mini invasive;
- extent of surgical resection;
- palliative surgery.

Results

The search terms returned 362 papers from the combined databases. Of these, 41 articles (including review, metanalysis, case reports, comments, and editorials) were included from the initial screen and the full text was reviewed for relevance; four reviews and three articles were excluded, because they did not report a clear correlation between follow-up duration and postsurgical epilepsy outcome.

Overall, we identified 34 articles that in total included 1,026 patients who received surgery for drug-resistant epilepsy associated with TSC. Collectively, age at surgery ranged from one month to 54 years. Mean age at surgery, based on 22 articles with available age data, was 8.41 years. Follow-up ranged from three months to 15 years.

▼ **Table 1.** Articles included in the review and general characteristics of the reported patients.

Study	Number of Pts	Mean age at surgery	Range of age at surgery	Mean FU	Range FU	Engel Ia (*n*)	Engel Ia (%)
Asano *et al.*, 2000 [60]	7	n.a.	1 y-9,5 y	n.a.	3 m- 2,4 y	5	71%
Karenfort *et al.*, 2002 [93]	8	9,9 y	6 m- 34,3 y	1,6 y	6 m-4,3 y	2	25%
Jarrar *et al.*, 2004 [40]	22	12,5 y	1 y-54 y	1 y	1 y	13	29%
			1 y-54 y	5 y	5 y	9	42%
Kagawa *et al.*, 2005 [61]	17	4,7 y	4 m-12,3 y	15 m	5 m-4,8 y	12	70%
Lachhwani *et al.*, 2005 [55]	17	11,6 y	2 m-31 y	3,6 y	1 y-15 y	11	65%
Jansen *et al.*, 2006 [44]	3	n.a.	n.a.	3 y	2 y-4 y	2	67%
Weiner *et al.*, 2006 [94]	21	4,4 y	7 m-16,6 y	2,5 y	6 m-6,2 y	13	62%
Jensen *et al.*, 2007 [21]	6	22,8 y	3 y-36 y	3 y	15 m-6,3 y	3	50%
Madhavan *et al.*, 2007 [33]	70	n.a.	n.a.	n.a.	n.a.	37	53%
Teutonico *et al.*, 2008 [41]	21	7.9 y	n.a.	6 y	6 m-15 y	11	50%
Moshel *et al.*, 2010 [95]	15	3,7 y	1,1 y-8 y	3,3 y	3m-90 m	9	60%
Wu *et al.*, 2010 [39]	18	5,5 y	0,7 y-17 y	4,1 y	1,7 y-8,5 y	12	67%
Ochi *et al.*, 2011 [96]	13	n.a.	1,1 y- 16 y	2,7 y	14 m- 5,8 y	8	62%
Kassiri *et al.*, 2011 [26]	10	n.a.	Pediatric	2 y	1 y-6 y	9	90%
Aboian *et al.*, 2011 [63]	6	3,9 y	0,7 y-13 y	4,4 y	2 y-9,5 y	3	50%
Ma *et al.*, 2012 [18]	12	6,5 y	2 y-15,5 y	n.a.	n.a.	8	67%
Mohamed *et al.*, 2012 [67]	17	n.a.	1,5 y-8,8 y	1,7 y	1 y–5,2 y	6	35%
Liu *et al.*, 2012 [69]	17	4,2 y	1,5 y-8 y	3 y	1,2 y-6 y	11	64%
Rubì *et al.*, 2013 [62]	3	n.a.	n.a.	n.a.	9 m-23 m	2	67%
Krsek *et al.*, 2013 [56]	33	4,4 y	0,1 y- 17,6 y	2 y	2 y	18	55%
Kargiotis *et al.*, 2014 [43]	11	n.a.	1 y-22 y	2,7 y	1 y-7 y	7	63%
Jahodova *et al.*, 2014 [51]	34	5.6 y	1 m-14 y	2 y	2 y	19	56%
Yogi *et al.*, 2015 [54]	23	5,5 y	0,9 y-20 y	4,2 y	0,5 y-9,1 y	10	43%
Fallah *et al.*, 2015 [38]	74	n.a.	3 m-18 y	1 y	1 y	48	65%
			3 m-18 y	2 y	2 y	37	50%
			3 m-18 y	3 y	3 y	33	45%
			3 m-18 y	4 y	4 y	32	43%
Arya *et al.*, 2015 [37]	37	6,2 y	1 y- 12 y	5,6 y	2 y-9 y	21	57%
Kannan *et al.*, 2016 [48]	10	5.4 y	2,4 y-13,3 y	3,3 y	10 m- 8,3 y	4	40%
Fujiwara *et al.*, 2016 [70]	14	5.9 y	2 y-16 y	n.a.	n.a.	7	50%
Liang *et al.*, 2017 [32]	51	n.a.	5 y-28 y	1 y	1 y	38	75%
			5 y-28 y	5 y	5 y	30	59%
			5 y-28 y	10 y	10 y	11	48%
Koptelova *et al.*, 2018 [97]	7	n.a.	4 y-16,9 y	2,3 y	1 y- 4 y	4	57%
Fohlen *et al.*, 2018 [30]	15	2.1 y	5 m-4,5 y	4,7 y	1,9 y-7,2 y	9	60%
Savini *et al.*, 2018 [42]	16	n.a.	n.a.	n.a.	n.a.	12	75%
Liu *et al.*, 2020 [50]	364	10,4 y	0.5 y–47 y	1 y	1 y	258	71%
				4 y	4 y	118	60%
				10 y	10 y	36	51%

▼ **Table 1.** Articles included in the review and general characteristics of the reported patients (continued).

Study	Number of Pts	Mean age at surgery	Range of age at surgery	Mean FU	Range FU	Engel Ia (*n*)	Engel Ia (%)
Neal *et al*., 2020 [31]	15	n.a.	n.a.	4,8 y	12.5 m-7,3 y	10	67%
Grayson *et al*., 2020 [89]	19	1.4 y	0.3-1.8 y	1.9 y	1-4 y	10	53%

Pts: patients, FU: follow-up, m: months, y: years.

Percentage of Engel Class Ia ranged from 29% to 90%. *Table 1* shows data according to the published studies.

Clinical findings: epilepsy phenotype and neuropsychiatric background

• *Epileptic spasms*

We analysed the occurrence of ES at the time of surgery, the age at seizure onset, and epilepsy duration.
The possible correlation between the presence of ES in TSC patients and postsurgical outcome was evaluated in four studies:
– two meta-analysis [19, 20];
– one systematic review [21];
– one multicentre study [33].

The occurrence of ES was frequently considered a possible pitfall in epilepsy surgery, in particular, the presence of ES at surgery was thought to be predictive of seizure freedom not being achieved [33]. However, this finding has not been supported by more recent meta-analyses/literature review, and no correlation was confirmed between the presence of ES and seizure outcome [19-21]. The lack of a correlation finding was consistent with other case series looking at postsurgical outcome of ES in various pathologies, including TSC: the overall seizure freedom rate was high, ranging from 61.3% to 74.6% [34, 35]. The occurrence of ES was associated with poor cognitive and behavioural outcomes, therefore, such patients should be promptly referred to epilepsy surgery [36].
Data on other seizure types are quite scarce and only the presence of tonic seizures (undetermined whether focal or generalized) has been associated with poor seizure outcome [21].

• *Age at seizure onset*

The effect of age at seizure onset on postsurgical outcome was evaluated in five studies:
– two retrospective single-centre studies [30, 37];
– two multicentre studies [33, 38];
– one meta-analysis [20].

In general, these studies found that later onset of seizures (more than 12 months [20, 33] was associated with higher seizure freedom rates.
This variable was also evaluated in a meta-analysis [20], that did not reveal a significant value in predicting postsurgical outcome.
Duration of epilepsy was evaluated in three studies:
– one single-centre study with longitudinal evaluation of patients [32];
– two retrospective single-centre studies [37, 39].

Short duration of epilepsy was also considered an important determinant of postoperative seizure freedom [30, 32, 33, 37, 38]. However, this variable was not analysed in any meta-analysis.
Similarly, higher pre-operative IQ has been reported to have positively influenced the overall postsurgical outcome [21, 32, 38, 40, 41].

Diagnostic procedures

Table 2 shows all diagnostic procedures that have been applied for the pre-surgical evaluation of drug-resistant patients with TSC in the publications. All studies included use of video-EEG and brain MRI.

• *Non-invasive neurophysiological procedures*

Video-EEG Video-EEG monitoring has been considered as mandatory in pre-surgical evaluation in TSC patients. The main parameters evaluated were interictal abnormalities, ictal seizure pattern, and semiology.
A detailed analysis of ictal scalp video-EEG in a cohort of 51 TSC patients was reported [42]. In this study, of the whole sample of patients, 16 were surgically treated and 75% were seizure-free after surgery. Focal seizures were the most frequent type (82%). Onset of seizures was characterized by non-motor focal signs with behavioural arrest in half of patients, and all forms (hyperkinetic, tonic, and clonic) of motor behaviour in the other half. Ictal EEG was characterized by a flattening or low-voltage fast activity evolving to rhythmic theta activity in 57% of patients, and by slow waves with rhythmic theta–delta activity and/

▼ **Table 2.** Diagnostic procedures applied in the different studies.

Study	Patients	V-EEG	Brain MR	DTI MRI	SPECT	FDG-PET	AMT-PET	HD EEG	MEG	GRIDS/ STRIPS	iECoG	SEEG
Asano *et al.*, 2000 [60]	7	x	x			x	x					
Karenfort *et al.*, 2002 [93]	8	x	x			x				x	x	
Jarrar *et al.*, 2004 [40]	22	x	x		x					x	x	
Kagawa *et al.*, 2005 [61]	17	x	x			x	x			x	x	
Lachhwani *et al.*, 2005 [55]	17	x	x									
Jansen *et al.*, 2006 [44]	3	x	x					x	x			
Weiner *et al.*, 2006 [94]	21	x	x		x	x			x	x		
Jansen *et al.*, 2007 [21]	6	x	x					x	x			
Madhavan *et al.*, 2007 [33]	70	x	x		x	x						
Teutonico *et al.*, 2008 [41]	21	x	x			x			x	x		x
Moshel *et al.*, 2010 [95]	15	x	x		x	x			x	x		
Wu *et al.*, 2010 [39]	18	x	x			x						
Ochi *et al.*, 2011 [96]	13	x	x						x	x		
Kassiri *et al.*, 2011 [26]	10	x	x									
Aboian *et al.*, 2011 [63]	6	x	x		x	x	x					
Mohamed *et al.*, 2012 [67]	17	x	x							x		
Liu *et al.*, 2012 [69]	17	x	x					x		x	x	
Ma *et al.*, 2012 [18]	12	x	x							x		
Krsek *et al.*, 2013 [56]	33	x	x		x	x				x	x	
Rubì *et al.*, 2013 [62]	3	x	x			x	x		x			x
Jahodova *et al.*, 2014 [51]	34	x	x		x	x				x	x	
Kargiotis *et al.*, 2014 [43]	11	x	x		x	x		x				
Yogi *et al.*, 2015 [54]	23	x	x	x		x						
Arya *et al.*, 2015 [37]	37	x	x		x	x			x	x		
Fallah *et al.*, 2015 [38]	74	x	x		x	x			x	x		
Fujiwara *et al.*, 2016 [70]	14	x	x							x		
Kannan *et al.*, 2016 [48]	10	x	x							x	x	
Koptelova *et al.*, 2017 [97]	7	x	x						x	x	x	
Liang *et al.*, 2017 [32]	51	x	x			x				x		
Savini *et al.*, 2018 [42]	16	x	x									x

▼ **Table 2.** Diagnostic procedures applied in the different studies (continued).

Study	Patients	V-EEG	Brain MR	DTI MRI	SPECT	FDG-PET	AMT-PET	HD EEG	MEG	GRIDS/ STRIPS	iECoG	SEEG
Fohlen *et al.*, 2018 [30]	15	x	x							x	x	x
Neal *et al.*, 2020 [31]	15	x	x			x	x	x	x			x
Liu *et al.*, 2020 [50]	364	x	x			x				x		x
Grayson *et al.*, 2020 [89]	19		x							x		x
Total	**1026**	**33**	**34**	**1**	**10**	**19**	**5**	**5**	**11**	**21**	**9**	**7**

V-EEG: video-EEG; MR: Magnetic resonance; DTI: diffusor tensor imaging; SPECT: single photon emission computed tomography; FDG-PET: F-18 fluorodeoxyglucose; positron emission tomography; AMT-PET: alpha methyl tryptophan positron emission tomography; HD-EEG: high-density EEG; MEG: magnetoencephalography; iECoG: intra-operative electrocorticography; SEEG: Stereo-EEG.

or diphasic spike–wave discharges in 21%; in 22% of patients, no clear focus was evident [42]. The second most frequent seizure type was ES (25%), which were clearly focal in 38% of cases. In 31% of ES, these were preceded or followed by a focal seizure. Generalized seizures (motor, atonic, or atypical absences) were rare (6%) [42].

The value of ictal EEG was also underlined in two meta-analysis [19, 20]. The presence of either focal interictal or ictal abnormalities concordant with the MRI lesion was a clear positive predictive factor for seizure freedom.

Source localization procedures Both MEG and high-resolution EEG (HR EEG) electromagnetic source imaging has been studied in TSC surgical candidates [43]. In most of the studies, source localization procedures used dipole modelling of interictal spikes. All studies were retrospective: the main aim was to correlate the localization of spikes with the supposed epileptogenic tubers (identified with other diagnostic tools) and surgical resection.

The largest study [44] compared MEG (151 channels) with HR EEG (85 channels) in 19 patients with TSC and concluded that MEG yielded sources were closer to tubers than HR EEG. The main limitation of this study was that only three patients had eventual operations. In operated patients from another study, the use of MEG was associated with good concordance (65%) with invasive ictal recordings [37].

The value of dipole analysis in HR EEG was examined in a pilot study with five patients. Perfect concordance was found between the resection and the dipole localization, and the overall Class 1 Engel outcome [43]. One notable caveat was that the dipole analyses were performed only after surgery; hence, inference on the predictive value of seizure freedom is inadvisable. Further evidence for the source localization procedure being of diagnostic value has been recently provided in a non-selected population of patients [45].

• *Neuroimaging*

Brain MRI is challenging in patients with TSC approaching epilepsy surgery evaluation.

Individual studies have focused on other features of tubers: size or localization [46], presence of calcification and/or "cyst-like appearance [47], and tuber-centre characteristics [48]. Each of these features has been suggested to be an indicator of epileptogenicity, but the only clear predictive factor of seizure freedom from these is the co-occurrence in a single tuber of bigger size and calcifications [49, 50]. Moreover, the presence of increased cortical thickness, grey-white-matter junction blurring, the abnormal gyration, and the transmantle changes are all highly predictive of epileptogenic tubers [51]. These alterations are not

only visible at the tuber centre but also in the perituberal tissue, suggesting that the tissue surrounding the epileptogenic tuber is also epileptogenic. Indirect confirmation of this hypothesis is the large number of seizure-free patients after tuberectomy plus corticectomy *versus* tuberectomy alone [49, 50].
In addition to delineating the resection margins in preoperative plans, accurate definition of TSC-lesion MRI has important implications for clinicians with respect to correlation of the clinical severity to the extent of cortical abnormality. For better tuber and perituberal cortex definition, studies [52, 53] have investigated the use of 7 Tesla MRI in patients with TSC and reported improved visualization of subtle lesions (not detected by the 3T MR) with clear delineation of the perituberal cortex. Diffuse tensor imaging (DTI) with apparent diffusion coefficient (ADC) [54] also seems promising for the identification of new morphological features in epileptogenic tubers. ADC values are clearly increased in epileptogenic tubers, with a 81% sensitivity and 44% specificity [54]. For both techniques, real-world clinical application studies are not yet available.

EEG-MRI concordance Concordance between EEG and MRI (both ictal and interictal) has been widely evaluated with respect to identifying epileptogenic tubers [19, 32, 55, 56]. As already reported above for EEG, previous meta-analysis reinforced the importance of EEG–MRI concordance as a predictive feature of postsurgical seizure freedom [19, 20]. These data were partially contradictory to subsequent reports, and no clear-cut correlations with long-term follow-up have yet been found [38, 50].

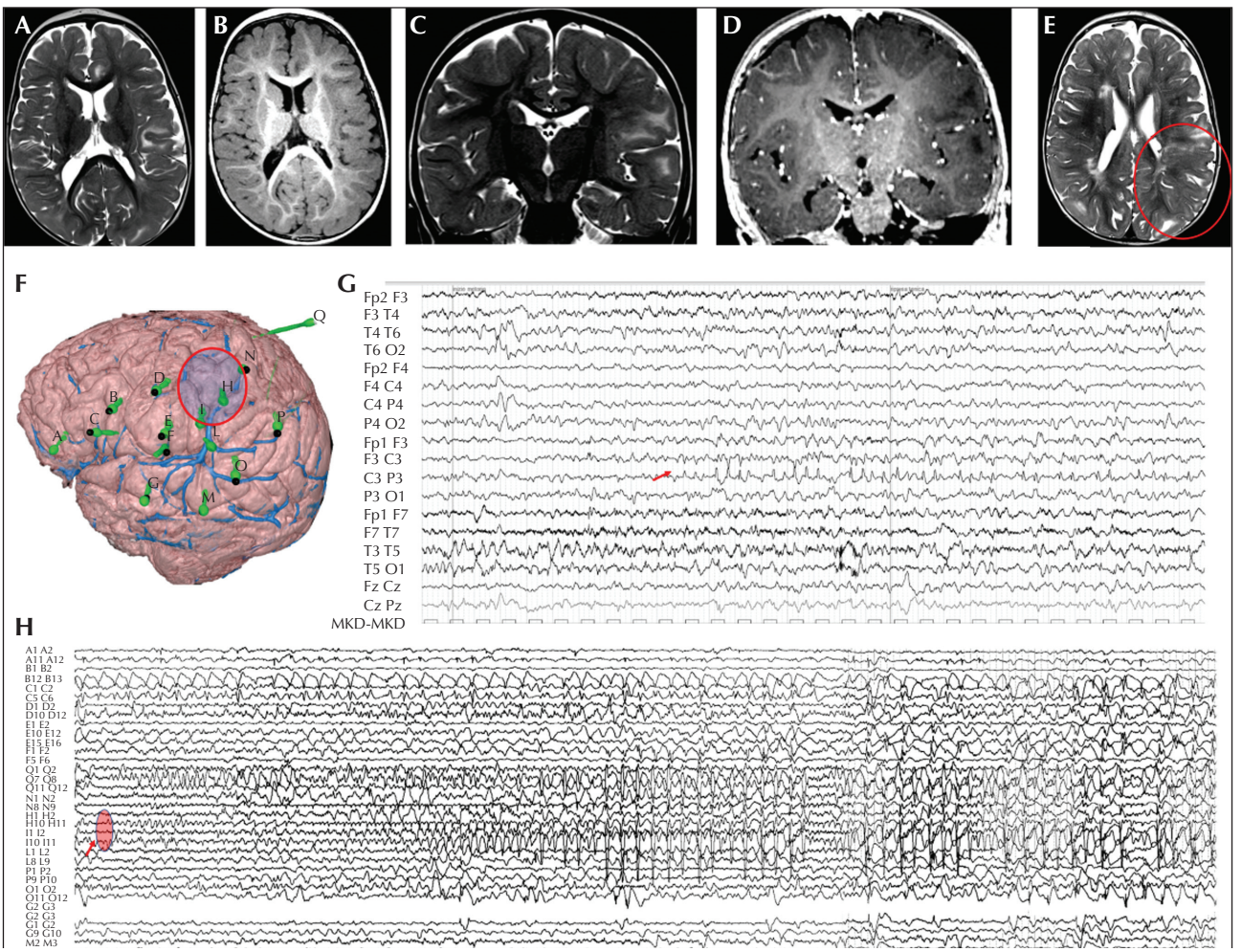
Positron emission tomography (PET) PET co-registered with MRI has frequently been used in the pre-surgical evaluation in patients with TSC. Two radiotracers are commonly used, ^{18}fluoro-2-deoxyglucose (FDG) and alpha-methyl-L-tryptophan (AMT). FDG is one the more commonly used in pre-surgical evaluations for patients with epilepsy - the epileptogenic lesion being hypometabolic [57]. In patients with TSC, however, both epileptogenic and non-epileptogenic tubers might display an increased hypometabolic volume [58]. For this reason, FDG PET results should be correlated with MRI findings (*e.g.*, ADC value) or neurophysiological results (*e.g.*, MEG source imaging). Such integrated evaluation seems to improve the localization of the epileptogenic tubers, allowing resective surgery and avoiding invasive recordings. Overall seizure freedom did not significantly differ based on an integrated evaluation of morphological and neurophysiological results compared to invasive recording data [39].
The use of AMT-PET was introduced by Chugani *et al*. [59] in 1998 and this approach showed good concordance between AMT-PET and intracranial EEG data (77% sensitivity and up to 100% specificity) [60, 61]. These results were subsequently partially confirmed by the Lyon team [62] who reported high specificity (100%), but low sensitivity (12%).

Single-photon emission computerized tomography (SPECT) Results from ictal SPECT and subtraction ictal SPECT co-registered to MRI (SISCOM) in patients with TSC have been described in two studies with a very limited number of patients and discordant results. Aboian *et al*. [63] reported on a cohort of six patients, of whom five had a dominant SISCOM focus, but only three were seizure-free, and in two, seizure freedom was associated with complete resection based on SISCOM hyperperfusion lesions. Within a sample of 11 patients who received surgery, pre-surgical SISCOM results were concordant with the resection area in four of seven seizure-free patients [43]. In the same study, FDG-PET was concordant in six of the seven seizure-free patients.

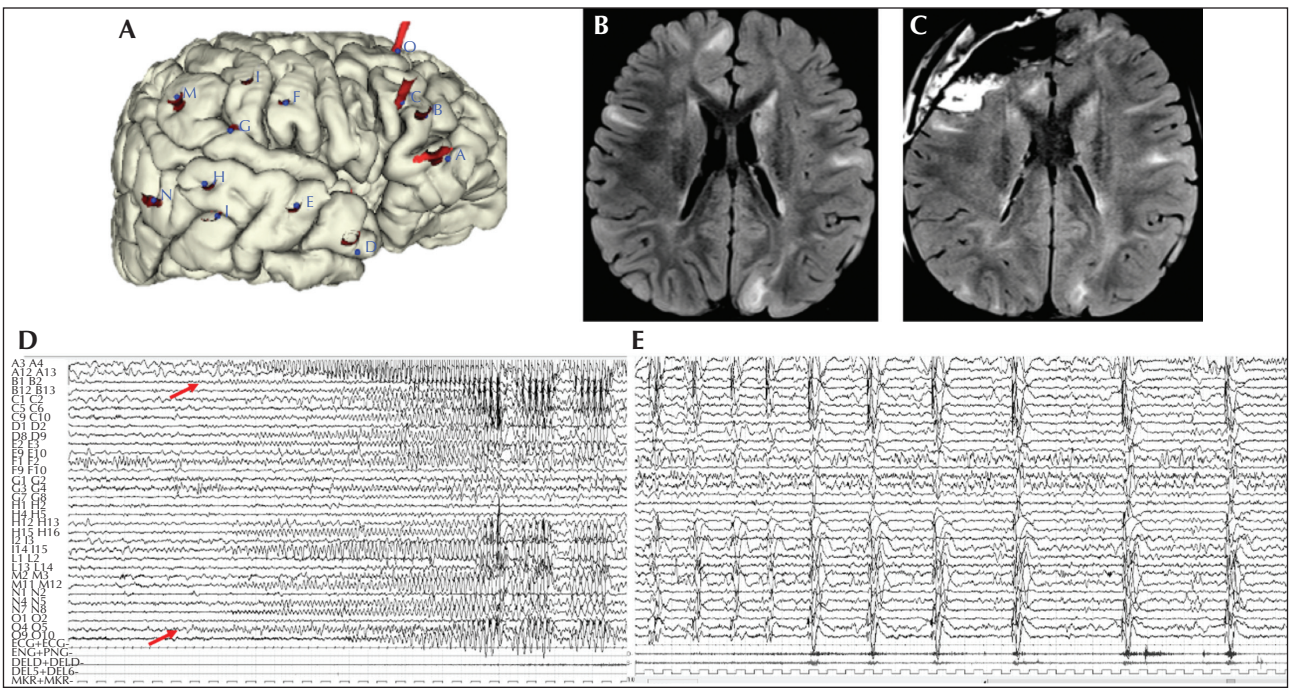
• *Invasive recordings*

Invasive recordings are mandatory in cases where the definition of the EZ remains ill-defined after review of non-invasive neurophysiological investigation and neuroimaging data [64]. The presence of a single, clear-cut lesion on brain MRI is the most valuable predictive factor of seizure freedom after surgery without invasive recordings [65]. However, the presence of multiple brain lesions with tuberous sclerosis is almost a certainty, therefore, invasive recordings are more frequently used in patients with drug-resistant epilepsies (*figures 1 and 2*).
Of 501 patients who underwent invasive recordings: 334 (66.7%) were studied with subdural grid/strip implantation, 89 (17.8%) with SEEG, and 78 (15.6%) underwent single-stage surgery after intra-operative electrocorticography.
Previously, whether the ictal discharge originates from the tuber or in the perituberal cortex in patients with TSC was in debate. Furthermore, a limitation to some studies was the lack of a definition for good spatial coverage in invasive studies [49]. A study from the Montreal Neurological Institute was one of the earliest to address the origins of ictal discharges based on both non-invasive and invasive (electrocorticography) recordings. From this study, the following was noted:

- some patients exhibited a focal organization of the EZ, however, others displayed multifocal or generalized interictal and ictal abnormalities that relied on a wider epileptogenic network;
- patients with a focal organization of the epileptogenic network shared the same neurophysiological features seen in FCD II, particularly interictal repetitive and continuous spikes;



■ **Figure 1.** Presurgical evaluation of a two-year-old patient with a *TSC2* genetic variant and drug-resistant epilepsy. Seizures started at the age of two months. Neurological examination revealed right hemiparesis and cognitive delay. The patient presented with both focal right hemiclonic seizures and focal asymmetric epileptic spasms with right arm prevalence. (A-E) Brain MRI at the age of 20 months. (A-D) Axial and coronal T2 and T1-weighted sequences showing multiple hyperintense areas on T2-weighted sequences and hypointense on T1-weighted sequences for bilateral tubers. (E) Parietal postcentral tuber marked with a circle, showing blurring of the grey-white matter, which was explored using intracranial electrodes (N, H, I) and involved the seizure onset. (F) Intracranial SEEG exploration of the left hemisphere using 15 electrodes: eight electrodes (D, E, F, N, H, I, L, Q) were used to explore the perirolandic tuberal area; three electrodes (A, B, C) for the anterior frontal region; two electrodes (G, M) for the superior temporal gyrus; and two (O, P) for the posterior parietal region. (G) Video-EEG recording showing a focal seizure, with paroxysmal rhythmic discharge of spikes and sharp waves with phase reversal at electrode C3. Clinically, the patient presented with chin contractions, reduced awareness, inconstantly associated with left eye deviation. (F) SEEG recording showing a focal seizure starting as theta rhythmic activity over electrodes Q, N, H, I, evolving into spike-and-wave complexes, mixed with sequences of fast activity. Clinically, the patient demonstrated a mild reduction in responsiveness during the initial ictal discharge, followed by a brief tonic contraction of the right side during the fast activity.



■ **Figure 2.** Presurgical evaluation and surgical approach in a five-year-old patient with a *TSC1* genetic variant. Epilepsy onset occurred at four months of age, with epileptic spasms without clear-cut clinical lateralization. Afterwards, the patient started to present with focal seizures characterized by right head deviation and diffuse tonic contraction (left>right), followed by subtle epileptic spasms (mild head deviation). Psychomotor development was moderately delayed, language was strongly delayed, and autistic features were evident. Video-EEG showed right multifocal continuous interictal epileptiform abnormalities. (A) Intracranial SEEG exploration of the right hemisphere using 18 electrodes: four electrodes (A, B, C, O) were used to explore the frontal lobe, both basal and dorsal surface; six electrodes (D, E, H, I, N, G) for the temporal lobe; and three electrodes (F, L, M) for the posterior parietal area. (B) Preoperative brain MRI showing multiple bilateral tubers with hyperintensity on FLAIR-weighted sequences. (C) Post-operative brain MRI showing that the resection area corresponded to the right fronto-basal region which was identified by the SEEG study. Three years post-surgery, the patient was seizure-free, with improvement in language and interaction. (D) The SEEG recording showing a focal seizure starting with a low-voltage fast discharge over electrodes B, C, O, followed by rhythmic theta activity at the same electrodes and over electrode A; soon after, the ictal discharge involved temporal electrodes (D, E, H, M, N) with spike and spike-and-wave complexes. (E) The focal seizure was followed by a cluster of epileptic spasms characterized by pseudorhythmic complexes of spikes, followed by a high-voltage slow wave, mixed with fast activity evident at electrodes A3-4. The clinical counterpart was subtle (mild bilateral muscular activation on polygraphic traces).

– and the main electrical abnormalities arose in the tuber itself [66].

More than 20 years later, the same results were confirmed using invasive recordings and a computational model of the EZ, referred to as the "epileptogenic index", in 18 patients with TSC who underwent SEEG [33]. In 53% of the studied cohort, the focal EZ was characterized by:

– a dominant tuber;
– a gradient of epileptogenicity from tuber centre to rim;
– and intra-tuber continuous interictal epileptic spikes.

In support of this theory on tuber origins of discharge, these patients achieved 80% Engel Class IA outcome with lesionectomy/tuberectomy. In the remaining patients, a complex epileptogenic network including involvement of the perituberal was evident with an apparently normal cortex; around 40% of these patients had a documented, clear-cut reduction of postsurgical seizure freedom [31].

The observation that the centre of the tuber seems to lead the ictal discharge (with only late perituberal diffusion) was the inference from the combined use of grids and depth electrodes when spatial sampling of

the tuber and perituberal cortex was optimal. The findings were provided from a series of 10 patients studied with invasive procedures, and the leading tubers from this report demonstrated the same neurophysiological features as seen with FCD II, with continuous interictal discharge in the tuber centre and low-voltage fast activity at ictal onset. Three of the 10 patients (30%) were seizure-free [48], which suggests that some patients had a more complex organization of the EZ [67].

The outcome is significantly different to what is expected for FCD II, however, we argue that the number of tubers and the presence of white matter-mediated connections might influence the epileptogenic network and consequently the overall post-surgical outcome.

Contradictory results were reported based on a similar mixed approach of grids and depth electrodes, and authors concluded that the perituberal cortex was also responsible for the epileptic discharge, and a FCD II-like organization of the tuber was not confirmed [18]. This discrepancy in results is probably due to both the extension of sampling [18,50] and the existence of different subgroups of patients; some with a FCD II-like/tuber-oriented EZ organization and others with a wider perituberal EZ [31, 66].

One-stage surgery guided by intra-operative electrocorticography (iECoG) is currently used and considered safe and effective in TSC patients, especially for those with a single seizure type, a single or one large tuber, and convergent electrophysiological data [15, 56, 68].

Some studies [33, 56, 69] showed that a single-stage surgical approach based on iECoG did not differ significantly in terms of post-surgical seizure outcome, compared with multistage approaches. However, in cases of multiple epileptogenic zones, or in subjects with overlapping epileptogenic and eloquent cortical areas, long-term invasive EEG remains mandatory and a multistage approach is requested.

More advanced neurophysiological methodologies, such as interictal and ictal high-frequency analysis, were attempted to better define the EZ in patients with TSC. Preliminary data reported that high frequency oscillations (HFOs) correlated well with the resected area in TSC, with around 70% sensitivity [70]. More studies are needed in this area given that patients with TSC seem to display a lower HFO rate when compared with patients with FCD, nodular heterotopia, and mesial temporal lobe sclerosis [71].

Type of surgery

- ***Resective surgery***

Of 1,026 patients included in this review, data on type of surgery and related outcome were available in 788 (76.8%). The mean follow-up duration was three years. *Table 3* shows the outcome in terms of seizure freedom based on type of surgery. Overall, 350 patients had a tuberectomy and 223 (63.7%) were seizure-free, 194 patients had a lobectomy of whom 134 (69%) were seizure-free, and 224 had a multilobar resection of whom 146 (65.1%) were seizure-free. Eight patients underwent hemispherotomy of whom six (75%) were seizure-free.

In surgical TSC series, significant variability in surgical techniques is evident and all have different seizure outcomes. Consequently, no consensus exists on whether patients with TSC should receive tuberectomy, tuber and perituberal cortex resection, or lobectomy. A previous meta-analysis suggested that lobectomies offer a higher degree of seizure freedom than tuberectomy [20]. These results were supported by recommendations from European experts that a resection beyond tuber margins would achieve a higher degree of seizure freedom [6].

In the largest cohort published to date [50], tuber with perituberal cortex resection and lobectomy resulted in significantly improved seizure outcomes compared with tuberectomy alone. Conversely, lobectomy was not superior to tuberectomy with perituberal resection, thus the final recommendation was to favour tuberectomy plus perituberal cortex. Whether this recommendation can be extended to every patient with TSC undergoing surgery is still debated. The positive results from tuberectomy in patients with a FCD II-like EZ suggest that a decision on surgical approach would be better made based on the pre-surgical results [31, 49]. *Figure 2* shows one example of a patient who received tuberectomy after invasive monitoring in which focal seizures and epileptic spasms were recorded.

Multi-staged epilepsy surgery with post-resection monitoring (PRM) has been proposed for patients with focal structural aetiologies, such as TSC, and FCD. One study performed a PRM with implanted subdural and depth electrodes for up to one week after surgery in 71 children (46 with TSC, 65%). Positive PRM was identified in 61 patients (86%) among the whole group, and in 41 of TSC patients (89%).

Fifty-five patients underwent a re-resection after PRM (77%) with an Engel Class I outcome in 65% after two years of follow-up. Of TSC patients, 63% had an Engel Class I outcome at one year of follow-up, and 56% after two years [72].

In most cases with re-resection, PRM revealed new clinical and subclinical activity at the margins of the resection cavity. In TSC patients, these findings seem to support the observation that perituberal cortex could be epileptogenic possibly due to the presence of microtubers in the perituberal parenchyma [73].

PRM therefore may be useful in order to uncover relevant additional information, such as residual activity at the margins of the resection cavity as well as unmasking additional seizure foci.

Further longitudinal studies are required to address

▼ **Table 3.** Surgical procedures in TSC patients.

Study	No. Pts	Tubers bilateral (Y/N)	Tuberectomy (seizure-free)	Lobectomy (seizure-free)	Multilobar resection (seizure-free)	Hemispherotomy (seizure-free)	Follow-up
Karenfort *et al.*, 2002 [93]	8	n.r.	4 (1, 25%)	1 (1, 100%)	1 (0)	2 (0)	6 m-4,3 y
Jarrar *et al.*, 2004[c] [40]	22	Y	8 (4, 50%)	0	0	0	1 y
	19	Y	7 (2, 28%)	0	0	0	5 y
Kagawa *et al.*, 2005 [61]	17	Y	0	1 (1, 100%)	13 (8, 62%)	3 (3, 100%)	5 m-4,8 y (15 m)
Lachhwani *et al.*, 2005 [55]	17	Y	1 (0)	12 (8, 67%)	4 (3, 75%)	0	1 y-15 y (3,6 y)
Jansen *et al.*, 2006 [44]	3	n.r.	3 (67%)	0	0	0	2 y-4 y (3 y)
Weiner *et al.*, 2006 [94]	21	Y	8 (5, 63%)	2 (2, 100%)	11 (7, 64%)	0	6 m-6,2 y (2,5 y)
Jansen *et al.*, 2007 [21]	6	Y	2 (1, 50%)	3 (1, 33%)	1 (1, 100%)	0	2 y-4 y (3 y)
Teutonico *et al.*, 2008 [41]	21	Y	21 (15, 71%)	0	0	0	6 m
	20	Y	20 (14, 70%)	0	0	0	1 y
	20	Y	20 (10, 50%)	0	0	0	2 y
	13	Y	13 (6, 46%)	0	0	0	5 y
	13	Y	13 (6, 46%)	0	0	0	6 y
Wu *et al.*, 2010 [39]	18	Y	0	9 (6, 67%)	8 (5, 63%)	1 (1, 100%)	1,7 y-8,5 y (4,1 y)
Moshel *et al.*, 2010 [95]	15	Y	15 (9, 60%)	0	0	0	3m-90 m (3,3 y)
Aboian *et al.*, 2011 [63]	6	Y	4 (2, 50%)	1 (1, 100%)	1 (0)	0	2 y-9,5 y (4,4 y)
Kassiri *et al.*, 2011 [26]	10	Y	5 (5, 100%)	5 (4, 80%)	0	0	1 y-6 y (2 y)
Ochi *et al.*, 2011 [96]	13	n.r.	1 (0)	3 (1, 33%)	9 (7, 78%)	0	14 m- 5,8 y (2,7 y)
Liu *et al.*, 2012 [69]	17	Y	7 (5, 71%)	0	10 (6, 60%)	0	1,2 y-6 y (3 y)
Mohamed *et al.*, 2012 [67]	17	Y	17 (6, 35%)	0	0	0	1 y–5,2 y (1,7 y)
Rubì *et al.*, 2013 [62]	3	Y	2 (2, 100%)	1 (0)	0	0	9 m-23 m
Krsek *et al.*, 2013[b] [56]	33	Y	n.r.	24 (13, 54%)	9 (4, 44%)	0	2 y
Kargiotis *et al.*, 2014 [43]	11	Y	2 (1, 50%)	5 (3, 60%)	4 (3, 75%)	0	1 y-7 y (2,7 y)
Arya *et al.*, 2015 [37]	37	Y	7 (5, 71%)	15 (7, 47%)	13 (7, 54%)	2 (2, 100%)	2 y-9 y (5,6 y)
Fujiwara *et al.*, 2016 [70]	14	Y	0	7 (4, 57%)	7 (4, 57%)	0	
Kannan *et al.*, 2016 [48]	10	N	10 (4, 40%)	0	0	0	10 m- 8,3 y (3,3 y)
Liang *et al.*, 2017 [32]	51	Y	26 (21, 81%)	15 (11, 73%)	10 (6, 60%)	0	1 y
	51	Y	26 (16, 62%)	15 (9, 60%)	10 (5, 50%)	0	5 y
	23	Y	10 (4, 40%)	8 (5, 63%)	5 (2, 40%)	0	10 y
Koptelova *et al.*, 2018 [97]	7	Y	3 (2, 67%)	2 (2, 100%)	2 (0)	0	1 y- 4 y (2,3 y)

▼ **Table 3.** Surgical procedures in TSC patients (continued).

Study	No. Pts	Tubers bilateral (Y/N)	Tuberectomy (seizure-free)	Lobectomy (seizure-free)	Multilobar resection (seizure-free)	Hemispherotomy (seizure-free)	Follow-up
Fohlen *et al.*, 2018 [30]	15	Y	6 (2, 33%)	1 (1, 100%)	8 (6, 75%)	0	1,9 y-7,2 y (4,7 y)
Neal *et al.*, 2020 [31]	15	[a]n.r.	11 (7, 64%)	4 (3, 75%)	0	0	12.5 m-7,3 y (4,8 y)
	364	Y	172 (117, 68%)	79 (62, 78%)	113 (79, 70%)	0	1 y
Liu *et al.*, 2020 [50]	196	Y	80 (47, 59%)	40 (28, 70%)	76 (43, 57%)	0	4 y
	71	Y	21 (9, 43%)	14 (11, 79%)	36 (16, 44%)	0	10 y
Grayson *et al.*, 2020 [89]	19	Y	15 (7, 47%)	4 (3, 75%)	0	0	1-4 y
Total	**788**		**350 (223, 63.7%)**	**194 (134, 69%)**	**224 (146, 65.1%)**	**8 (6, 75%)**	

Y: yes, N: no, Pts: patients, n.r.: not reported, m: months, y: years. a.13 bilateral implants. b. In this study, only lobar and mulitlobar resection were considered. c.Two patients underwent callosotomy and were therefore excluded from this table; in 12 patients, the type of surgery was classified as unilobar/multilobar and patients were excluded from the evaluation of results.

this question.

- ***Mini-invasive non-resective surgical treatment***

Magnetic resonance-guided laser interstitial thermal therapy (MRgLITT) is increasingly used in epilepsy surgery due to high precision, less invasiveness, and short hospital stay [74, 75]. Few reports are available on its use in patients with TSC. Two studies investigated the postsurgical outcome of using either a single or multi-staged approach. Preliminary data indicate an overall seizure freedom of between 43% and 67% [75, 76].

Limitations of MRgLITT include the inability to treat large lesions or irregular lesions adjacent to major blood vessels. To place the laser probe for LITT, stereotaxic procedures are required, which classically involve head fixation with cranial pins. This creates a relative minimum age limit of two years old because it demands a mature skull and fused cranial sutures. One study [77], however, has reported the use of a frameless navigation technique that allows the application to be used for younger patients.

Similar to radiofrequency ablation, MRgLITT allows for real-time monitoring of the extent of tissue ablation, and thus allows for immediate visual feedback [78]. Compared with tuberectomies or lobectomies, MRgLITT provides several advantages, including lower complication rates and decreased length of hospital stay, for example, the average length of stay in hospital was seven days when TSC therapy necessitated a craniotomy [74].

To date, few data are available specifically correlated with long-term seizure outcome. However, the alternative of a minimally invasive approach such as MRgLITT broadens the option of surgical treatment to include patients with reduced quality of life, who previously would not have met the criteria for open surgery [75].

Studies with a larger population and with longer follow-up are needed to confirm the efficacy of this technique.

- ***Palliative treatments***

Vagal nerve stimulation (VNS) has been investigated in patients with TSC. Data on its efficacy are based on small series of patients from different centres.

We found extensive data on 52 TSC patients who were treated with VNS [79-82]. In published studies with only a single patient report available, responders were considered with at least 50% seizure reduction at last follow-up. The average responder rate based on these collective reports was 73%, with 4% of patients being seizure-free [79-84]. Despite these promising results, the role of VNS in patients with TSC needs to be better defined based on larger studies with a longer follow-up period.

Corpus callosotomy (CC) is a palliative surgery for

patients with drug-resistant epilepsy that cannot be treated by resective surgery, and has been suggested to be especially suitable for patients with falls caused by epileptic seizures [85]. Few data have been published that focus on TSC patients. The most recent study reported a 43% seizure freedom rate in seven patients with TSC who received CC alone [86]. Other reports have used a combined approach that included cortical resection and CC. In particular, Liang *et al*. [32] reported that out of 11 patients with TSC, 55% achieved seizure freedom following CC plus resection surgery, and Liu *et al*. [69] reported data for seven surgical cases with ES secondary to TSC with 43% gaining seizure freedom.

Data related to deep brain stimulation (DBS) in TSC patients are scare. Only one case report was recently published regarding the use of DBS of the anterior thalamic nucleus [87]. After a follow-up of 15 months, a significant reduction in seizure frequency was reported. Being a single case, this result can only be considered as anecdotal and more data should be provided in order to understand whether DBS might be considered as an alternative treatment in TSC patients.

Overall outcome

In the majority of published surgical series, no longitudinal data are reported, and follow-ups range from a few months to several years. Regarding the evaluation of outcome, we focused on studies with a minimum follow-up of one year. Results from the studies were expressed as either longitudinal data or data reported over an average follow-up period. Longitudinal data were available from seven studies; overall seizure freedom was reported at between 65% and 75% at one year and between 48% and 51% after 10 years. In 21 of 28 studies, data regarding outcome were expressed as averages; seizure freedom ranged from 70% at one year to 57% at five years, which is the longest follow-up duration reported (*table 4*).

Overall outcome was previously also analysed in two meta-analysis and one systematic review, reporting 229 [20], 181 [19], and 170 [21] patients, respectively. Considering that different statistical approaches were used (systematic review and individual data analyses), the results are relatively consistent. Seizure freedom at one year was reported at 59% [20], 56% at two years [19], and 59% at four years [21]. An important issue to be considered is the relationship between seizure outcome and duration of follow-up. For those studies in which surgically-treated TSC patients were longitudinally followed, a progressive reduction in seizure freedom rates was evident, similar to that reported for other structural aetiologies [88]. The reason for increased seizure recurrence over time is probably related to diffuse epileptic/pro-epileptic pathologies and, in most cases, further surgery does not affect the final negative outcome [88]

The association between epilepsy and neurodevelopmental outcome in TSC has been repeatedly explored. Consistently, poor cognitive outcome is associated with earlier seizure onset, increased seizure severity, and presence of infantile spasms (Jansen *et al*., 2008; Chu-Shore *et al*., 2009) [8, 24].

Considering these aspects, early evaluation for a surgical option for drug resistant epilepsy in TSC should be considered, as the degree of post-operative seizure outcome correlates with improvement in cognition and quality of life [31, 37]. Despite this consideration, systematic assessment of the impact of surgery on neurodevelopmental outcome in the TSC population is lacking. A recent study [89] confirmed the association between ongoing seizure activity and developmental decline and established preliminary support for mitigation of this trajectory through early epilepsy surgery.

In this study was evaluated the possible effect of early epilepsy surgery (before the age of two years) in TSC patients, comparing their neurodevelopmental trajectory, through adaptive and language scores, with a group of non-operated patients with refractory epilepsy. A favourable surgical outcome was associated with increased receptive and expressive language sub scores, therefore they hypothesized that early surgery could positively affect neurodevelopmental trajectory [89].

Discussion

Our critical review highlights that postsurgical seizure freedom rates in patients with TSC are between 60% and 65% [19-21], however, these results seem not to be durable over time, with a decrease in seizure freedom over longer follow-up periods to 46-51%. Among the diagnostic pre-surgical tools, brain MRI and long-term video-EEG monitoring remain the most used non-invasive techniques, presumably due to the variable and lower accuracy reported in FDG and AMT-PET studies [61, 62]. Better delineation and evaluation of TSC epileptogenesis may be achieved by invasive recordings, especially SEEG [31, 48].

Longer prospective studies are needed to highlight the most predictive factors of postsurgical outcome in patients with TSC.

Despite the use of targeted antiepileptogenic drugs, which reduces the overall number of drug-resistant patients, more than half of patients with TSC still present with persistent seizures, and we still are not able to predict the patients who respond better to treatment.

Growing evidence from metanalyses suggests that surgery is associated with a 55%-60% rate of seizure

▼ **Table 4.** Epilepsy surgery outcome at different time points.

OUTCOME		1 year			2 years			3 years			]4 years			5 years			10 years		
Study	Pts Tot	Pts	SF	%	Pts	SF	%	Pts	SF	%	Pts	SF	%	Pts	SF	%	Pts	SF	%
Karenfort *et al.*, 2002 [93]	8				8	2	25												
Jarrar *et al.*, 2004* [40]	20	20	13	65										19	9	47			
Lachhwani *et al.*, 2005 [55]	17							17	11	65									
Kagawa *et al.*, 2005 [61]	17	17	12	70															
Jansen *et al.*, 2006** [44]	3							3	2	67									
Weiner *et al.*, 2006 [94]	21							21	13	62									
Jansen *et al.*, 2007** [21]	6							6	3	50									
Teutonico *et al.*, 2008* [41]	21	21	14	70	20	10	50							13	6	46			
Wu *et al.*, 2010 [39]	18										18	12	67						
Moshel *et al.*, 2010 [95]	15							15	9	60									
Aboian *et al.*, 2011 [63]	6										6	3	50						
Ochi *et al.*, 2011 [96]	13				13	8	62												
Kassiri *et al.*, 2011 [26]	10				10	9	90												
Liu *et al.*, 2012 [69]	17							17	11	64									
Mohamed *et al.*, 2012 [67]	17				17	6	35												
Krsek *et al.*, 2013** [56]	33				33	18	55												
Kargiotis *et al.*, 2014 [43]	11				11	7	63												
Jahodova *et al.*, 2014** [51]	34				34	19	56												
Yogi *et al.*, 2015 [54]	23										23	10	43						
Arya *et al.*, 2015 [37]	37													37	21	57			
Fallah *et al.*, 2015* [38]	74	74	48	65	74	37	50	74	33	45	74	32	43						
Kannan *et al.*, 2016 [48]	10							10	4	40									
Koptelova *et al.*, 2017** [97]	7				7	4	57												
Liang *et al.*, 2017* [32]	51	51	38	75										51	30	59	23	11	48
Fohlen *et al.*, 2018 [30]	15				15	9	60												
Liu *et al.*, 2020* [50]	364	364	258	71							197	118	60				71	36	51
Neal *et al.*, 2020** [31]	15													15	10	67			
Grayson *et al.*, 2020** [89]	19				19	10	53												

Pts: patients, SF: seizure-free. *Longitudinal studies. **Outcome provided at a specific time point (not intended to be an average).

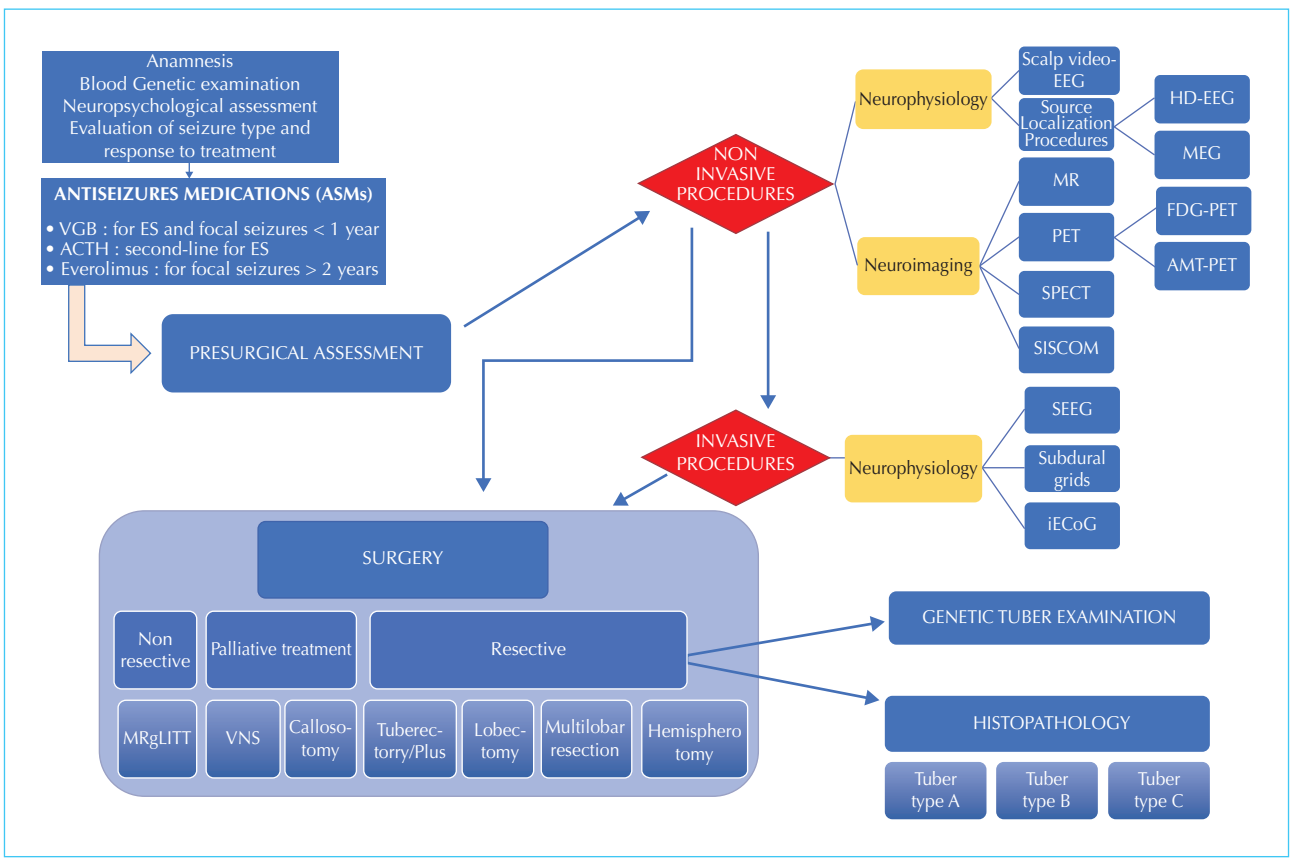
freedom. Despite this, clear agreement on who is the best candidate to be studied for surgical treatment has not been forthcoming, based on either non-invasive or invasive tools.

Given the complexity and the multifocal nature of epileptogenic networks in TSC, all patients should be referred to a dedicated paediatric epilepsy centre to receive pre-surgical evaluation from a multi-disciplinary epilepsy surgery team. Currently, pre-surgical evaluation is recommended "after the failure of two AEDs, even before ES occur and even with interictal epileptiform activity outside the selected area for resection, or when seizures are highly stereotyped on video-EEG with a predominant focus or even in the presence multifocal and bilateral lesions" [6].

Figure 3 shows our proposal for a diagnostic and interventional algorithm for patients with TSC and drug-resistant epilepsy. In the pre-surgical workup of patients with TSC, the mandatory first step is a careful evaluation of epilepsy history, neuropsychological baseline assessment and, if possible, a genetic examination. Subsequently, long-term scalp video-EEG monitoring is needed to characterize the seizure type(s) and evaluate seizure semiology and the hemispheric onset of ictal discharges. Furthermore, electroclinical and radiological correlation should be performed, including MRI evaluation of tuber morphology and localization. Other possible radiological tools (PET, SPECT, SISCOM) have proven to be less accurate in defining the epileptogenic tuber.

A radiological classification of tubers [90], based on MRI features within the tubers and in the subcortical white matter adjacent to the tuber, has been proposed and three tuber types (A, B, C) are identified. Type A tubers are characterized by mild hyperintensity signals on T2/FLAIR-weighted images and isointensity on T1. Type B tubers are hyperintense on T2/FLAIR-weighted images and hypointense on T1. Type C tubers are hyperintense on T2-weighted images but display heterogeneous hypersignal on FLAIR images and hypointense on T1. Type C tubers are more frequently correlated to the EZ (86%) and are more frequently characterized by specific electrical patterns that resemble focal cortical dysplasia (FCD)-type II [31].

Three distinct histopathological tuber profiles have been proposed [91] based on the degree of calcifications, dysmorphic neurons, and giant cells: Type A is characterized by a low density of giant cells and dysmorphic neurons;



■ **Figure 3.** Diagnostic and interventional algorithm for patients with TSC and drug-resistant epilepsy.

Type B by a high density of giant cells and dysmorphic neurons; and Type C by a high density of giant cells, dysmorphic neurons, and calcification. The latter two are associated with brain MRI features typical of the dysplastic cortex, such as a thickened cortex, a blurred grey-white-matter border, and the presence of a transmantle sign.

Direct surgery may be possible in patients with good electroclinical and MRI correlation. Invasive monitoring with intracranial electrodes is often mandatory in more complex cases, and bilateral explorations can be necessary to define the EZ and the area to resect. Due to source-localization techniques, better location of the EZ in patients with TSC is now possible, with consequential expectation for better outcomes in terms of seizure freedom and cognitive performance.

Despite previous debate on the role of the tuber or perituberal area on seizure onset, recent studies combining strip, grid, and tuber depth electrodes favour the notion that seizures arise from tubers, specifically the tuber centre rather than the perituberal cortex. This evidence supports a tuber-oriented surgical approach, although many surgical techniques are currently used and there is no clear consensus on the relative merit of each. However, resections beyond tuber borders (*tuberectomy plus* and *lobectomy*) are likely to lead to better seizure control.

The possible role of the perituberal area in epileptogenicity has also been studied at the histopathological level. Ruppe *et al*. [92] studied histological and immunohistochemical features of both brain MRI-identified epileptogenic tubers and perituberal areas and reported that tubers demonstrated severe disruption of cortical lamination, the presence of pS6-positive dysplastic neurons and giant cells, an overall increase in mTORC1 and decrease in mTORC2 activity, increased axonal connectivity and growth, and hypomyelination. Perituberal cortex presented similar histological, immunohistochemical, and molecular features, even if such findings were overall milder than that found in tubers. These data support the idea that perituberal tissues also show dysplastic features with dysregulated mTOR signalling.

To date, no clear-cut data are available on the correlation between histopathological findings and intracranial EEG features or postsurgical outcome.

We can assume that "tuberectomy plus" will allow for the best seizure and developmental outcome, since it ensures complete EZ resection with a lower level of surgical radicality relative to lobectomy. As a future approach, consideration of MRgLITT for the treatment of TSC is worthwhile based on the few data available, because this is a minimally invasive procedure that may well improve the burden of epilepsy. Some limitations to MRgLITT should be considered; small tubers can be ablated, calcified tubers are not suitable for this treatment, and this procedure is not approved currently for children under the age of two years.

One of the limitations of this review is that literature data did not allow to clearly establish which is the most appropriate surgical approach in TSC patients with different syndromic entities. We strongly believe that the surgical approach in TSC patients should be individualized and not only the major type of seizure (*i.e.* focal seizures versus epileptic spasms), but also the specific syndromic condition (*i.e.* patients presenting with West syndrome, Lennox-Gastaut syndrome, *etc.*) should be considered. Future studies should aim to address how the surgical approach might be different based on syndromic classification of TSC patients.

The pre-surgical and surgical approaches in patients with TSC and drug-resistant epilepsy are clearly challenging, mostly because of the number of tubers and the complex epileptogenic network which is responsible for the epileptogenic zone. Therefore, the questions of who, when, and what are still difficult to answer, and additional work is needed in order to better understand this complex condition.

Conclusion

Some uncertainties remain with respect to who, when, and what to treat, and which is the more appropriate surgical procedure. A tailored approach centred on the individual patient and discussed within the epilepsy surgery team should always be preferred, due to the heterogeneous nature of TSC patients. Hence, general recommendations are difficult to make. Notwithstanding the need for case-by-case evaluation, early surgery is always recommended in patients with TSC and postsurgical outcome should be evaluated not only for seizures but also regarding cognitive abilities and behaviour, which are both of paramount importance to patients and caregivers. ■

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TEST YOURSELF

(1) Is epilepsy in patients with tuberous sclerosis surgical remediable?

(2) How can SEEG help in delineating the epileptogenic zone?

(3) Which is the best surgical approach?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".