CLINICAL EXPERIENCE

Current role of surgery for tuberous sclerosis complex-associated epilepsy

Nicola Specchio¹ | Giusy Carfi Pavia¹ | Luca de Palma¹ | Alessandro De Benedictis² | Chiara Pepi¹ | Marta Conti¹ | Carlo Efisio Marras² | Federico Vigevano³ | Paolo Curatolo⁴

¹Rare and Complex Epilepsy Unit, Department of Neurosciences, Bambino Gesù Children’s Hospital, IRCCS, Rome, Italy
²Neurosurgery Unit, Department of Neurosciences, Bambino Gesù Children’s Hospital, IRCCS, Rome, Italy
³Department of Neurosciences, Bambino Gesù Children’s Hospital, IRCCS, Rome, Italy
⁴Child Neurology and Psychiatry Unit, Systems Medicine Department, Tor Vergata University, Rome, Italy

Correspondence
Nicola Specchio, Department of Neurosciences, Bambino Gesù Children’s Hospital, IRCCS, Piazza S. Onofrio 4, 00165, Rome, Italy.
Email: nicola.specchio@opbg.net

Received: 5 November 2021
Accepted: 30 December 2021

ABSTRACT
Tuberous sclerosis complex (TSC) is a rare multisystem, autosomal dominant neurocutaneous syndrome in which epilepsy is the most common of several neurological and psychiatric manifestations. Around two thirds of patients develop drug-resistant epilepsy for whom surgical resection of epileptogenic foci is indicated when seizures remain inadequately controlled following trial of two antiseizure medications. The challenge with presurgical and surgical approaches with patients with TSC is overcoming the complexity from the number of tubers and the multiplex epileptogenic network forming the epileptogenic zone. Data suggest that seizure freedom is achieved by 55%–60% of patients, but predictive factors for success have remained elusive, which makes for unconfident selection of surgical candidates. This article presents three different cases as illustrations of the potential challenges faced when assessing the suitability of TSC patients for epilepsy surgery.

KEYWORDS
Epilepsy, Everolimus, Imaging, Prognostics, Surgery, Tuberous sclerosis complex (TSC)

INTRODUCTION
Tuberous sclerosis complex (TSC) is a rare neurocutaneous syndrome (one in 6000–22,000 live births)¹,² for which the major morbidity is usually neurologic, though virtually any organ system can be affected.³ Approximately 85% of patients carry a pathogenic variant of the TSC1 or TSC2 genes, which cause excessive activation of the “mammalian target of rapamycin” (mTOR) signaling pathway through elevated activity of mTOR.⁴ A common signaling node of the mTOR pathway mutations seems to be mTOR complex 1 (mTOR and raptor, its binding partner),⁵ which has strong association with the characteristic hamartomas, tuberous sclerosis-associated neuropsychiatric disorders (TAND),⁶ and epilepsy.⁴

Epilepsy is the most common (80%–90% of patients)⁷ of a large spectrum of neurological and psychiatric manifestations of patients with TSC, which also includes intellectual disability, behavioral abnormalities, and autism spectrum disorder.⁸ Deaths are most commonly also from status epilepticus and sudden unexpected death in epilepsy. The
type of seizures experienced by patients with TSC are
diverse (e.g., focal and generalized motor seizures, epilepti-
tic spasms [ES], tonic, atonic, and tonic-clonic seizures),
but 62.5%–73% of patients experience seizures during the
first year of life.9,10 The most common seizure-type during
this first year is ES and 75% of these patients become drug
resistant—proportionally greater than patients without a
history of ES of whom a still sizeable 40% develop drug-
resistant epilepsy.10 Notably, patients with early-onset ES
develop also experience a higher degree of intellectual disability
than patients experiencing either late-onset ES or other
seizure types.11–13

Although around two thirds of patients eventually develop
drug-resistant epilepsy,10 early treatment of epilepsy with
antiseizure medications (ASMs) is reported to improve
longer term outcomes,14 and controlled epilepsy is associated
with reduced symptoms of autism. The recommended
first-line treatment in early-onset seizures is vigabatrin,
which stops TSC-related infantile spasms in up to 95%
of cases.8 Combination of vigabatrin with hormonal ther-
apy has been reported to provide even better long-term
outcomes.1

In general, between 52% and 100% patients with TSC are
treated with a combination of two or more ASMs. Combin-
ing multiple mechanisms of action (valproic acid, carbam-
azeptine, topiramate, lamotrigine, and vigabatrin) is pro-
dent in most cases to cover the multitude of seizure types.14
Nevertheless, an overly aggressive approach with ASMs
should be avoided as cognitive and behavioral side effects
can worsen TAND, which is challenging for most parents.
Despite the introduction of targeted drugs for TSC, such as
vigabatrin and mTOR inhibitors, we are still unable to pre-
dict the patients who can benefit from these treatments, and
more than half of patients still present seizures.8 Cannabidi-
lol is an option as it has been associated with halving
seizure frequency compared with placebo in a double-blind
randomized clinical trial.15

An effective nondrug treatment for epilepsy recommended
during the early stages is ketogenic diet (KD),16 the mecha-
anism for which has been suggested to be mTOR path-
way inhibition due to carbohydrate depletion.17 Vagal nerve
stimulation is also a consideration in patients unsuited to
epilepsy surgery, with about half reducing their seizure fre-
cuency by at least 50%.18

Resective surgery is an important treatment option that is
currently underused.19 Indication for considering surgery
are seizures remaining inadequately controlled following
trial of two ASMs. Surgery (resective or palliative) was
performed in only 10.7% of patients with focal seizures
and in 6.4% of patients with infantile spasms of the 1852
patients with epilepsy in the international “TuberOus SCle-
rosis registry to increase disease Awareness” (TOSCA).20

In comparison, mTOR inhibitors were prescribed in 7.7%
of patients with focal seizures and 5.5% of patients with
infantile spasms.

Data on surgical series revealed that seizures freedom
can be reached in 55%–60% of patients, with early inter-
ventions and accurate localization of the epileptogenic
region.21,22 Even if with surgery seizure freedom is not
reached, tailored surgical resection of epileptogenic foci
was still reported to improve seizure frequency by >90% in
18% of patients.21,22 Stereoelectroencephalography-directed mag-
etic resonance-guided laser interstitial thermal therapy
(SEEG-directed MRgLITT) is a minimally invasive tech-
nique in development that shows promise.24

Planning epilepsy surgery for TSC is challenging due to
the presence of multiple lesions (tubers). Furthermore, debate
continues on whether the “epileptogenic tuber” includes
the surrounding altered cortex. Accurate localization of the
epileptogenic network should be achieved to the limit per-
mitted from using standard procedures complicated by mul-
tiple tubers. Understandably, the approach varies consider-
ably between centers, depending on the clinical focus, scalp
or invasive electroencephalography (EEG), and functional
neuroimaging.21 The current recommendation is to identify
the target tuber with consideration to avoiding multifocal
and even bilateral resection.8

The aim of this article is to present three different cases as
illustrations of the potential challenges faced when assess-
ning the suitability of TSC patients for epilepsy surgery.

RESULTS

Case 1

A 6-year-old boy, born at term with prenatal diagnosis of
left ventricular rhabdomyosarcoma and subsequent diagno-
sis of TSC (TSC1 mutation), was referred for considera-
tion of surgery. During the neonatal period, depigmented mac-
cules were noted on his left leg and right side. His overall
development was delayed and he showed signs of behav-
ioral disorder. Seizures began at 3 months of age with infan-
tile spasms characterized by flexing of both upper arms and
trunk and stiffening of lower limbs.

The first brain magnetic resonance imaging (MRI) was
suggestive of bilateral cortical tubers and multiple
subependymal nodules (Figure 1A,B). Seizures were
partially responsive to vigabatrin, adrenocorticotropic hor-
monc (ACTH), and carbamazepine. At 11 months of age,
frequency and semiology of seizures had worsened, with
daily seizures then characterized by stiffening of bilateral
upper and lower limbs and head deviation toward the right.
The first video-EEG monitoring showed an interictal EEG
characterized by numerous multifocal abnormalities in the
right hemisphere (Figure 1D) and a right focal ical pattern.
These correlated with episodes of generalized hypertonia followed by a cluster of spasms (Figure 1D). MRI confirmed multiple cortical tubers in the left hemisphere. Mild improvement of seizure frequency was observed with valproic acid and steroids, and he was successfully reduced to vigabatrin as monotherapy.

Presurgical evaluation with SEEG monitoring at age 2 years showed that the epileptogenic zone (EZ) was in the right fronto-temporal lobe with early involvement of the orbital region (electrode A) (Figure 1E). Based on these clinical, neurophysiological, and radiological data, a right anterior frontal lobectomy was performed.

Post surgery, the boy remained seizure-free after 18 months of follow-up while still undergoing therapy with vigabatrin. He improved both intellectually and behaviorally, and an interictal EEG showed only rare right abnormalities.

Case 2

A 4-year-old girl with prenatal diagnosis of cardiac rhabdomyoma, ipomelanotic macules, and angiofibromas has been followed since surgery. Despite a negative family history of epilepsy, genetic testing found deletion of TSC2.

At 1 month of age, she presented with daily right myoclonic seizures. Multiple cortical tubers and subependymal nodules were detected in MRI (Figure 2A,B). At first neurological evaluation, the video-EEG showed a focal seizure—characterized by grimace, palpebral blinking, and oral automatism—that correlated to a left centro-temporal discharge (Figure 2D). Seizures were partially responsive to levetiracetam, vigabatrin, carbamazepine, and topiramate.

At psychological evaluation, she was diagnosed with a psychomotor development delay and deficiency in acquired functional language.

At 2 years old, she underwent presurgical SEEG monitoring with a left-side implantation that showed an EZ in opercular (electrodes L, P, and M) and parietal (electrode N) regions (Figure 2E) during seizures characterized by right eye clonic jerks with involvement of the right arm.

At 3 years old, she underwent resection of the right parietal lobe, including the epileptogenic tuber (Figure 2C).

At the most recent follow-up at 16 months after surgery, she was in Engel II and her EEG showed left central abnormalities with ASMs reduced but not fully withdrawn.

Case 3

An 11-year-old girl with prenatal diagnosis of cardiac rhabdomyoma revealed by echocardiography at second trimester (7 months of pregnancy) has been followed post surgery. MRI revealed multiple tubers, primarily in the left parietal lobe (Figure 3A). Genetic analysis found a de novo mutation in TSC1, which confirmed the diagnosis of tuberous sclerosis with neurologic, cardiac, and renal...
FIGURE 2 (A) Preoperative axial T2-weighted brain MRI showing multiple bilateral tubers with hyperintense signal over the fronto-temporo-parietal regions. (B) Left T1-weighted sagittal sequence, showing large hypointense tuber over the posterior suprasylvian region. (C) Postsurgical FLAIR sequence, showing the focal resected area in the suprasylvian posterior operculum, excluding the insula. (D) Interictal video-EEG with left fronto-temporal epileptiform abnormalities, with contralateral synchronous diffusion. (E) SEEG seizure recording: rhythmic spike and wave complexes over electrodes P, M, and L (shown in the square) with clinical correlate of right eyelid clonic jerks, then evolving in low-voltage fast activity over the same electrodes (hypomotor phase, pointed out with the arrow), then again more diffused spike and wave complexes with right face and arm clonic jerks. EEG, electroencephalography; FLAIR, fluid attenuated inversion recovery; MRI, magnetic resonance imaging; SEEG, stereoelectroencephalography.

FIGURE 3 (A) FLAIR-weighted MRI with bilateral tubers, among which the most prominent over the left parietal lobe. (B) Postsurgical FLAIR sequence showing the parietal resection. (C) Wakefulness interictal video-EEG with left parietal and vertex epileptiform abnormalities. (D) Video-EEG recording of left parietal focal seizure, with rhythmic theta activity over C3–P3 and anterior vertex, evolving in focal spike and sharp waves discharge. EEG, electroencephalography; FLAIR, fluid attenuated inversion recovery; MRI, magnetic resonance imaging.
involvement. The neurological symptoms had appeared early as daily focal right hemiclonic seizures and asymmetric spasms (Figure 3C,D). Seizures were treated with vigabatrin, carbamazepine, and ACTH with partial response.

When she was 8 months old, refractory epilepsy meant she underwent a left parietal tuber resection at the Rothschild Hospital in Paris (Figure 3B). After surgery, she was in Engel class I for several years and so drug cessation was attempted when she was 9 years old; however, this was stopped due to considerable interictal abnormalities appearing on the EEG.

At 7 years old, she had a loop recorder implanted after a syncopal event. Cardiac follow-up revealed the presence of bilateral ventricular rhabdomyoma and confirmed the absence of asystole.

The radiological follow-up remained invariant. At last neurophysiological follow-up, the EEG showed an asymmetric activity for the presence of lower activity in the left hemisphere, but she was still seizure-free. She was in the range of moderate intellectual impairment.

**DISCUSSION**

Meta-analysis of the growing published evidence suggest that 55%–60% of postsurgery patients with TSC achieve freedom from seizures. However, the practical development of policy from this statistic is limited, because clear agreement on who are the best candidates for surgical treatment remains unclear, even after assessment with invasive as well as noninvasive tools.

The most widely evaluated tool for identifying epileptogenic tubers has been the concordance between EEG and MRI (both ictal and interictal).\(^{25-27}\) The potential of EEG–MRI concordance as a predictive feature of postsurgical seizure freedom has been supported by meta-analysis.\(^{28}\) Nevertheless, these hypothesis-generating data were only partially corroborated by subsequent reports and no clear-cut correlations have yet been found with long-term follow-up.\(^{23,29}\)

Presurgical evaluation in patients with TSC has commonly also included positron emission tomography (PET) co-registered with MRI. More complex cases often necessitate invasive monitoring with intracranial electrodes, and bilateral explorations are frequently required to define the EZ and the area to resect. Locating the EZ is now aided by source-localization techniques, which is expected to improve outcomes in terms of seizure freedom and cognitive performances.

Age at onset on seizure has been evaluated as a predictor of postsurgical outcome in four studies—two retrospective single-center studies\(^{30,31}\) and two multicenter studies\(^{29,32}\)—and assessed by meta-analysis.\(^{33}\) In general, these studies suggested that onset of seizures after the first year of life was associated with a greater proportion of seizure freedom, but support was weak by meta-analysis.\(^{33}\) Many studies have also suggested that shorter duration of epilepsy is a determinant of postsurgical seizure freedom,\(^{27,30-32,34,35}\) though these have not yet been assessed by meta-analysis. Similarly, better overall postsurgical outcome has been associated with higher IQ prior to surgery.\(^{27,35-37}\)

The origin of seizure onset being within the tuber area (rather than perituberal cortex) has received support from recent studies combining strip, grid, and tuber depth electrodes. Consequently, this evidence favors a tuber-oriented surgical approach, though diverse surgical techniques remain with no consensus on the relative merits for each. Intuitively, resections beyond tuber borders (tubectomies plus and lobectomy) are likely to result in better seizure control on average.

In the majority of published surgical series, assessments were at only one follow-up time point, ranging from a few months to several years post surgery. Longitudinal data were available from seven studies, which collectively suggest seizure freedom is achieved by 65%–75% at 1 year, which reduces to 48%–51% after 10 years of follow-up. In 21 of 28 studies, data regarding the outcome are expressed as average\(^{31}:\) seizure freedom ranges from 70% at 1 year to 57% at 5 years, which is the longest follow-up duration reported.\(^{21}\)

The postsurgical follow-up was quite favorable in our three reported cases, being two of them in Engel class I (Case 1 and Case 3) and one in Engel class II (Case 2). Despite rare, isolated, and short focal seizures in Case 2, we decided to partially decrease ASMs to reduce the burden of treatment: her seizure frequency remained stable.

Brain MRI is challenging in patients with TSC, and individual studies have focused on diverse features (size or localization,\(^ {38}\) presence of calcification and/or cyst-like appearance,\(^ {39}\) tuber-center characteristics\(^ {40}\)), with each potentially associated with epileptogenicity. The strongest predictive factor of seizure freedom after surgery is the co-occurrence within a single tuber of both bigger size and calcifications,\(^ {23,29}\) or without invasive recordings, a single, clear-cut lesion.\(^ {41}\) As TSC is almost always associated with multiple brain lesions, invasive recordings are more frequently used than with other etiologies in patients with drug-resistant epilepsies.

The challenge with the presurgical and surgical approaches with patients with TSC and drug-resistant epilepsy is overcoming the complexity from the number of tubers and the multiplex epileptogenic network forming the EZ.
Despite the use of targeted antiepileptogenic drugs, which has reduced the overall number of drug-resistant patients, more than half of patients with TSC still present persistent seizures and we are still unable to predict reliably the patients who will respond best post surgery.

ACKNOWLEDGMENTS

We thank Dr. David Macari for English text editing and Prof. Olivier Delalande for the support given in the surgical treatment of Case 3.

CONSENT FOR PUBLICATION

Consent for publication was obtained from patients/caregivers.

CONFLICT OF INTEREST

Nicola Specchio has received support from Livanova and Biomarin, and has served as a paid consultant for Livanova. Paolo Curatolo has served as a paid consultant for Novartis. The remaining authors report no conflict of interest.

REFERENCES

1. Curatolo P, Moavero R, de Vries PJ. Neurological and neuropsychiatric aspects of tuberous sclerosis complex. Lancet Neurol. 2015;14:733-745. DOI: 10.1016/s1474-4422(15)00069-1

2. Ebrahimi-Fakhari D, Mann LL, Poryo M, Graf N, von Kries R, Heinrich B, et al. Incidence of tuberous sclerosis and age at first diagnosis: new data and emerging trends from a national, prospective surveillance study. Orphanet J Rare Dis. 2018;13:117. DOI: 10.1186/s13023-018-0870-y

3. Amin S, Lux A, Calder N, Laugharde M, Osborne J, O’callaghan F. Causes of mortality in individuals with tuberous sclerosis complex. Dev Med Child Neurol. 2017;59:612-617. DOI: 10.1111/dmcn.13352

4. Curatolo P, Mechanistic target of rapamycin (mTOR) in tuberous sclerosis complex-associated epilepsy. Pediatr Neurol. 2015;52:281-289. DOI: 10.1016/j.pediatrneurol.2014.10.028

5. Curatolo P, Moavero R, van Scheppingen J, Aronica E. mTOR dysregulation and tuberous sclerosis-related epilepsy. Expert Rev Neurother. 2018;18:185-201. DOI: 10.1080/14737175.2018.1428562

6. de Vries PJ, Belousova E, Benedik MP, Carter T, Cottin V, Curatolo P, et al. TSC-associated neuropsychiatric disorders (TAND): findings from the TOCSA natural history study. Orphanet J Rare Dis. 2018;13:157. DOI: 10.1186/s13023-018-0901-8

7. Northrup H, Krueger DA. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol. 2013;49:243-254. DOI: 10.1016/j.pediatrneurol.2013.08.001

8. Curatolo P, Nabbout R, Lagae L, Aronica E, Ferreira JC, Feucht M, et al. Management of epilepsy associated with tuberous sclerosis complex: updated clinical recommendations. Eur J Paediatr Neurol. 2018;22:738-748. DOI: 10.1016/j.ejpn.2018.05.006

9. Davis PE, Filip-Dhima R, Sideridis G, Peters JM, Au KS, Northrup H, et al. Presentation and diagnosis of tuberous sclerosis complex in infants. Pediatrics. 2017;140:e2016040. DOI: 10.1542/peds.2016-4040

10. Chu-Shore CJ, Major P, Camposano S, Muzykewicz D, Thiele EA. The natural history of epilepsy in tuberous sclerosis complex. Epilepsia. 2010;51:1236-1241.

11. French JA, Lawson JA, Yapici Z, Ikeda H, Polster T, Nabbout R, et al. Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study. Lancet. 2016;388:2153-2163. DOI: 10.1016/S0140-6736(16)31419-2

12. Curatolo P, Franz DN, Lawson JA, Yapici Z, Ikeda H, Polster T, et al. Adjunctive everolimus for children and adolescents with treatment-refractory seizures associated with tuberous sclerosis complex: post-hoc analysis of the phase 3 EXIST-3 trial. Lancet Child Adolesc Health. 2018;2:495-504. DOI: 10.1016/S2352-4642(18)30099-3

13. Capal JK, Bernardino-Cuesta B, Horn PS, Murray D, Byars AW, Bing NM, et al. Influence of seizures on early development in tuberous sclerosis complex. Epilepsy Behav. 2017;70:245-252. DOI: 10.1016/j.yebeh.2017.02.007

14. Cusmai R, Moavero R, Bombardieri R, Vigevano F, Curatolo P. Long-term neurological outcome in children with early-onset epilepsy associated with tuberous sclerosis. Epilepsy Behav. 2011;22:735-739. DOI: 10.1016/j.yebeh.2011.08.037

15. Thiele EA, Bebin EM, Bhathal H, Jansen FE, Kotulska K, Lawson JA, et al. Add-on cannabidiol treatment for drug-resistant seizures in tuberous sclerosis complex: a placebo-controlled randomized clinical trial. JAMA Neurol. 2021;78:285-292. DOI: 10.1001/jamaneurol.2020.4607

16. Kossoff EH, Zupec-Kania BA, Avuin S, Ballaban-Gil KR, Christina Bergqvist AG, Blackford R, et al. Optimal clinical management of children receiving dietary therapies for epilepsy: updated recommendations of the International Ketogenic Diet Study Group. Epilepsia Open. 2018;3:175-192. DOI: 10.1002/epi4.12225

17. Boison D. New insights into the mechanisms of the ketogenic diet. Curr Opin Neurol. 2017;30:187-192. DOI: 10.1097/WCO.0000000000000432

18. Major P, Thiele EA. Vagus nerve stimulation for intractable epilepsy in tuberous sclerosis complex. Epilepsy Behav. 2008;13:357-360. DOI: 10.1016/j.yebeh.2008.04.001

19. Romanelli P, Verdecchia M, Rodas R, Seri S, Curatolo P. Epilepsy surgery for tuberous sclerosis. Pediatr Neurol. 2004;31:239-247. DOI: 10.1016/j.pediatrneurol.2004.05.012

20. Nabbout R, Belousova E, Benedik MP, Carter T, Cottin V, Curatolo P, et al. Epilepsy in tuberous sclerosis complex: findings from the TOCSA study. Epilepsia Open. 2019;4:73-84. DOI: 10.1002/epi4.12286

21. Specchio N, Pepi C, de Palma L, Moavero R, De Benedictis A, Marras CE, et al. Surgery for drug-resistant tuberous sclerosis complex-associated epilepsy: who, when,
and what. Epileptic Disord. 2021;23:53-73. DOI: 10.1684/epd.2021.1253
22. Vannicola C, Tassi L, Barba C, Boniver C, Cossu M, de Curtis M, et al. Seizure outcome after epilepsy surgery in tuberous sclerosis complex: results and analysis of predictors from a multicenter study. J Neurol Sci. 2021;427:117506. DOI: 10.1016/j.jns.2021.117506
23. Liu S, Yu T, Guan Y, Zhang K, Ding P, Chen L, et al. Resective epilepsy surgery in tuberous sclerosis complex: a nationwide multicentre retrospective study from China. Brain. 2020;143:570-581. DOI: 10.1093/brain/awz411
24. Stellon MA, Cobourn K, Whitehead MT, Elling N, McClintock W, Oluigbo CO. “Laser and the Tuber”: thermal dynamic and volumetric factors influencing seizure outcomes in pediatric subjects with tuberous sclerosis undergoing stereoelectroencephalography-directed laser ablation of tubers. Childs Nerv Syst. 2019;35:1333-1340. DOI: 10.1007/s00381-019-04255-4
25. Krsek P, Jahodova A, Kyncl M, Kudr M, Komarek V, Jezdik P, et al. Predictors of seizure-free outcome after epilepsy surgery for pediatric tuberous sclerosis complex. Epilepsia. 2013;54:1913-1921. DOI: 10.1111/epi.12371
26. Lachhwani DK, Pestana E, Gupta A, Kotagal P, Bingaman W, Wyllie E. Identification of candidates for epilepsy surgery in patients with tuberous sclerosis. Neurology. 2005;64:1651-1654. DOI: 10.1212/01.WNL.0000160389.93984.53
27. Liang S, Zhang J, Yang Z, Zhang S, Cui Z, Cui J, et al. Long-term outcomes of epilepsy surgery in tuberous sclerosis complex. J Neurol. 2017;264:1146-1154. DOI: 10.1007/s00415-017-8507-y
28. Zhang K, Hu WH, Zhang C, Meng FG, Chen N, Zhang JG. Predictors of seizure freedom after surgical management of tuberous sclerosis complex: a systematic review and meta-analysis. Epilepsy Res. 2013;105:377-383. DOI: 10.1016/j.eplepsyres.2013.02.016
29. Fallah A, Rodgers SD, Weil AG, Vadera S, Mansouri A, Connolly MB, et al. Resective epilepsy surgery for tuberous sclerosis in children: determining predictors of seizure outcomes in a multicentre retrospective cohort study. Neuroradiology. 2015;7:517-524; discussion 524. DOI: 10.1227/NEU.0000000000000875
30. Fohlen M, Taussig D, Ferrand-Sorbets S, Chipaux M, Dori-son N, Delandane O, et al. Refractory epilepsy in preschool children with tuberous sclerosis complex: early surgical treatment and outcome. Seizure. 2018;60:71-79. DOI: 10.1016/j.seizure.2018.06.005
31. Arya R, Tenney JR, Horn PS, Greiner HM, Holland KD, Leach JL, et al. Long-term outcomes of resective epilepsy surgery after invasive presurgical evaluation in children with tuberous sclerosis complex and bilateral multiple lesions. J Neurosurg Pediatr. 2015;15:26-33. DOI: 10.3171/2014.10.PEDS14107
32. Madhavan D, Schaffer S, Yankovsky A, Arzimanoglou A, Renaldo F, Zaroff CM, et al. Surgical outcome in tuberous sclerosis complex: a multicenter survey. Epilepsia. 2007;48:1625-1628. DOI: 10.1111/j.1528-1167.2007.01112.x
33. Zhang K, Hu WH, Zhang C, Meng FG, Chen N, Zhang JG. Predictors of seizure freedom after surgical management of tuberous sclerosis complex: a systematic review and meta-analysis. Epilepsy Res. 2013;105:377-383. DOI: 10.1016/j.eplepsires.2013.02.016
34. Wu JY, Salamon N, Kirsch HE, Mantle MM, Nagarajan SS, Kurelowech L, et al. Noninvasive testing, early surgery, and seizure freedom in tuberous sclerosis complex. Neurology. 2010;74:392-398. DOI: 10.1212/WNL.0b013e3181ce5d9e
35. Fallah A, Weil AG, Sur S, Miller I, Jayakar P, Morrison G, et al. Epilepsy surgery related to pediatric brain tumors: Miami Children’s Hospital experience. J Neurosurg Pediatr. 2015;16:675-680. DOI: 10.3171/2015.4.PEDS14476
36. Jarrar RG, Buchhalter JR, Raffel C. Long-term outcome of epilepsy surgery in patients with tuberous sclerosis. Neurology. 2004;62:479-481. DOI: 10.1212/01.wnl.0000106947.18643.1d
37. Jansen FE, van Huffelen AC, Algra A, van Nieuwenhuizen O. Epilepsy surgery in tuberous sclerosis: a systematic review. Epilepsia. 2007;48:1477-1484. DOI: 10.1111/j.1528-1167.2007.01117.x
38. Ellingson BM, Hirata Y, Yogi A, Karavaeva E, Leu K, Woodworth DC, et al. Topographical distribution of epileptogenic tubers in patients with tuberous sclerosis complex. J Child Neurol. 2016;31:636-645. DOI: 10.1177/0883073815609151
39. Gallagher A, Chu-Shore CJ, Montenegro MA, Major P, Costello DJ, Lyczkowski DA, et al. Associations between electroencephalographic and magnetic resonance imaging findings in tuberous sclerosis complex. Epilepsy Res. 2009;87:197-202. DOI: 10.1016/j.eplepsires.2009.09.001
40. Kannan L, Vogrin S, Bailey C, Maixner W, Harvey AS. Centre of epileptogenic tubers generate and propagate seizures in tuberous sclerosis. Brain. 2016;139:2653-2667. DOI: 10.1093/brain/aww192
41. Martinez-Lizana E, Fauser S, Brandt A, Schuler E, Wiegand G, Dostokam S, et al. Long-term seizure outcome in pediatric patients with focal cortical dysplasia undergoing tailored and standard surgical resections. Seizure. 2018;62:66-73. DOI: 10.1016/j.seizure.2018.09.021