



Original Article

## Usefulness of Intraoperative ultrasound for cortical dysplasia type I treatment - A single-center experience

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### ABSTRACT

**Background:** Focal cortical dysplasias (FCD) cause a subgroup of malformations of cortical development that has been closely linked to cause drug intractable epilepsy. Attaining adequate and safe resection of the dysplastic lesion has proved to be a viable option to achieve meaningful seizure control. Of the three types of FCD (types I, II, and III), type I has the least detectable architectural and radiological abnormalities. This makes it challenging (preoperatively and intraoperatively) to achieve adequate resection. Intraoperatively, ultrasound navigation has proven an effective tool during the resection of these lesions. We evaluate our institutional experience in surgical management of FCD type I using intraoperative ultrasound (IoUS).

**Methods:** Our work is a retrospective and descriptive study, where we analyzed patients diagnosed with refractory epilepsy who underwent IoUS-guided epileptogenic tissue resection. The surgical cases analyzed were from January 2015 to June 2020 at the Federal Center of Neurosurgery, Tyumen, only patients with histological confirmation of postoperative CDF type I were included in the study.

**Results:** Of the 11 patients with histologically diagnosed FCD type I, 81.8% of the patients postoperatively had a significant reduction in seizure frequency (Engel outcome I-II).

**Conclusion:** IoUS is a critical tool for detecting and delineating FCD type I lesions, which is necessary for effective post-epilepsy surgery results.

**Keywords:** Epilepsy, Intraoperative ultrasound, Lesion resection

### INTRODUCTION

Proliferation of undifferentiated cells in the neuro-epithelium, migration of neuroblasts, cell differentiation, and cortical organization highlights the hallmark phases in the organization of the cortical mantle. Impairment of any of these processes usually results in malformations of

cortical developments (MCDs) which may manifest a form of focal cortical dysplasia (FCD).<sup>[1-9]</sup> Between 30% and 50% of pediatric patients, with intractable epilepsy, have been attributed to histologically diagnosed FCD.<sup>[5]</sup> After two unsuccessful anti-epileptic drug (AED) trials, neurosurgical resection has shown to be an effective option in patients diagnosed with FCDs. It has been observed that 75% of FCD patients are rendered seizure-free after surgery.<sup>[10]</sup>

In the recent past, studies have shown a strong correlation between: (1) different histological subtypes and (2) MRI positivity of FCD lesions to the surgical outcome.<sup>[3]</sup> Most authors have proven that MRI positive FCD with balloon cells (Taylor type, Palmini type 2b) has the most favorable outcome.<sup>[2,3,10,11]</sup> However, very little has been done to correlate FCD type I lesions to the surgical outcome.<sup>[6]</sup> This could be because FCD type I can affect multiple lobes, has prominent lobar hypoplasia, and is associated with less prominent gray/white matter junction blurring and signal changes primarily in white matter, all of which make preoperative surgical screening and intraoperative procedure very challenging.<sup>[4,7]</sup> In this article, we evaluate and describe our – single-center experience in applying intraoperative ultrasound (IoUS) navigation in aiding the surgical management of FCD type I with regard to the surgical outcome.

## MATERIALS AND METHODS

### Data collection

We sought institutional approval (Federal Center of Neurosurgery, Tyumen, Russia) for the use of IoUS as our neuronavigational tool during epilepsy surgery. The study model was to retrospectively analyze and descriptively report the patients who had been diagnosed with refractive epilepsy and underwent IoUS-guided epileptogenic tissue resection from January 2015 to June 31, 2020 with subsequent postoperative histological confirmation of FCD type I. In instances where histological results were inconclusive, specimens were sent to an independent histology laboratory for confirmation.

### Inclusion criteria

Patients included had to satisfy the following criteria: (1) be confirmed with drug-resistant epilepsy, following correctly prescribed and adherently taken two AEDs; (2) seizures, depicted by either scalp or invasive electro-encephalogram (EEG), the latter employing either subdural or invasive electrodes; (3) have had brain MRI imaging; (4) histologically confirmed FCD type I; and (5) postoperative follow-up  $\geq 6$  months.

### Exclusion criteria

Exclusion from this study was based on the following: (1) the patients had other subtypes of histologically-confirmed

FCD (either II or III); (2) had other lesions that could cause epilepsy; and (3) were lost to follow-up.

## Imaging

### MRI

Our epilepsy surgery team evaluated the MRI images in conjunction with an experienced neuro-radiologist and neuro-epileptologist. Characteristic elements on MRI that was sought for included: decreased T1 or moderately increased T2/Flair white matter signal changes; blurring of the gray-white matter junction; cortical and hippocampal atrophy (may or may not manifest in FCD Type I); and any signal changes in anatomical zones that correspond with EEG findings. 3T MRI was also implored in the event initial MRI images which were void of the latter elements. In the event, 3T MRI did not highlight any pathological findings; it was regarded as “MR negative.”

### EEG

Invasive sphenoidal, cortical, or in-depth electrodes were placed in individual patients for localization and lateralization when deemed necessary. All patients underwent long-term video-electroencephalography (EEG) monitoring, using either a Nicolet One 32-channel device (stationary) (USA), bedside EEG system Nicolet ONE 16-channel and 32-channel (USA) device, a BE Plus (128-channel) EBNeuro/Ates (Italy) device, a Cadwell Easy III 64-channel device (USA), or invasive video-ECOG-monitoring.

### Neuro-epileptologist and pediatric reviews

All patients were reviewed by a neuro-epileptologist. In the pediatric population, a pediatrician was implored to review the patients.

### Surgery

We employed navigational (FlexFocus 800 Ultrasound Machine BK Medical, Denmark) IoUS in all patients. Surgery was led by the first author. Implementation was IoUS conducted after the craniotomy in phases (duration in time on average); a) before dural opening (duration 30 s—1 min), after dural opening (duration 30 s), post lesion resection (duration 30 s—1 min). The application of IoUS was intended to: (1) localize dysmorphic brain tissue before and after opening the dura mater, thereby circumventing brain shift once the dura is opened; (2) localize the pathological focus; (3) determine the structure and echogenicity of dysplastic tissue in relation to the surrounding normal brain; (4) delineate the contours of the abnormal/pathological tissue; (5) measure the dimensions of dysplasia; and (6) evaluate the effectiveness

of IoUS to accurately delineate the area of resection, to optimize postoperative outcome.

Microsurgical removal of epileptogenic tissue was performed, under the guide of IoUS following the boundaries of the lesion. When dysplastic tissue was close to eloquent areas, mapping of the cerebral cortex and tracts was performed by neuro-stimulation, using motor and somatosensory evoked potentials. Dysplastic lesion was, then, resected within the mapped parameters to preserve motor and sensory function. Residual dysplastic tissue in close engulfing eloquent areas was purposefully left to avoid possible undesired postoperative neurological deficit.

Postoperatively, all resected brain tissues were sent for histological examination by an experienced pathologist within our institution and classified according to the scheme published by the International League Against Epilepsy. On discharge, patients were followed up in the outpatient clinic after 1 month, in the 3<sup>rd</sup> month, then the 6<sup>th</sup> and finally yearly. In special instances, reviews could be carried out through online, mobile phone, or email inquiries.

## RESULTS

### Demographics

All patients that were admitted had intractable epilepsy and had not undergone prior epilepsy surgery. Eleven patients with histologically diagnosed FCD type I met inclusion criteria. The median age of the patients who underwent surgery was 12-years-old (2–35 years of age). Focal seizures were most frequent (63.6%) and generalized spasms presented in 36.4% of the patients. During the median follow-up period of 18 months (11–60 months), 81.8% of the patients postoperatively had a significant reduction in seizure frequency (Engel outcome I–II) [Table 1]. Patients that had preoperative neurological deficits on presentation had either symptomatic improvement postoperatively or non-progressive sequelae.

### EEG

On scalp EEG recordings, interictal abnormalities were characterized by rhythmic spike and polyspike discharge's mimicking “ictal-like” activity which increased during sleep. Interictal and ictal discharges were focal, regional, and bilateral. Sphenoidal electrodes were placed in 4 patients, while subdural electrodes were implanted in four patients and in-depth electrodes in 3.

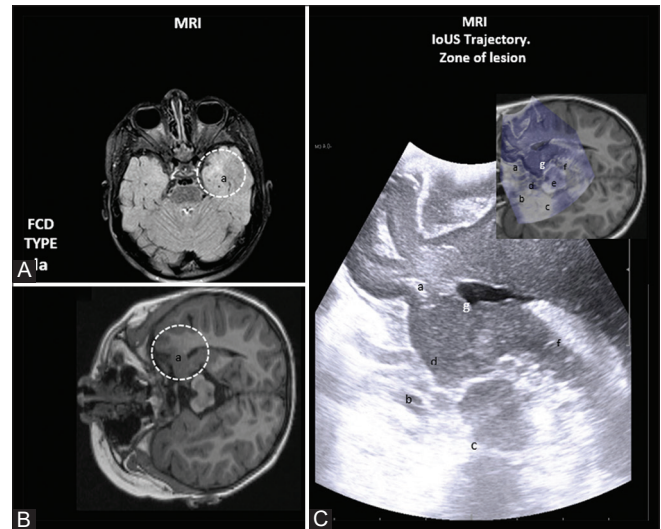
### MRI

MRI characteristics for each of the included patients were evaluated. Contrast enhancement or mass effect was not seen in any of the patients. Nine of the 11 patients had absent transmantle sign, cortical focal thickening and hyper

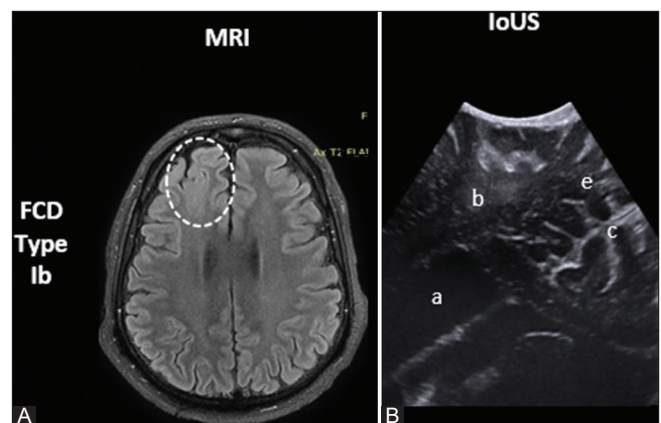
intensity, cortical–subcortical prolongation in T2WI, and fluid-attenuated inversion recovery. These patients were deemed as MRI “Negative.” Three patients were deemed MRI “Positive.” The MRI anatomical positive distribution patterns were in the occipital, temporal lobe, and frontal lobes.

### IoUS

Appreciation of the images depicted on IoUS was largely by the ability to highlight hyper echoic abnormalities. Anatomical location of these ultrasound abnormalities



**Figure 1:** FCD TYPE Ia A and B showing MRI Flair in Axial view (original and simulated (intraoperative) position) depicting affected zone of Lt Temporal lobe FCD Type Ia (Dashed lines). C: Highlighting combined MRI and IoUS trajectory to the zone of FCD lesion clearly depicting adjacent anatomical structures. a- Lt Temporal lobe FCD Type Ia., c - Cerebral peduncles, d - Hippocampus, e - Parahypocampus, f- choroid plexus, g - Lt temporal horn of the lateral ventricle, b - amygdala.



**Figure 2:** FCD TYPE Ib A - MRI Flair in Axial view depicting affected zone of RT frontal FCD Type Ib (Dashed lines). B: Highlighting IoUS FCD Lesion with related anatomical structures: a- Rt anterior horn of lateral ventricle, b- FCD Type Ib, c- Interhemispheric Fissure, e Superior frontal gyrus.

Table 1: Demographics and post-operative outcome.

Patient#	Sex	Age years	Diagnosis	Vedio EEG electrodes (Interictal scalp/Invasive ictal pattern)	Pre-OND	Post-OND	Operation	Histology	F/P	Seizure type/rate Prior OT	Seizures Post OT	Engle outcome
1	F	3	Right frontal lobe epilepsy	Scalp (C4, C3, F3, T3) Invasive Subdural (C3, F3, T3)	No	No	Microsurgical left lisionectomy	FCD Type Ic.	12 months	Focal Seizures. 2-3 p/week	0-1 p/3 m	II
2	F	12	Right occipital L focal cortical dysplasia	Scalp Sphenoid	No	No	Right occipital Lobe lesionectomy	FCD (Blumcke Type Ic)	18 month	Focal seizures 5-7 p/week	0-1/Year	I
3	M	35	Right mesial temporal sclerosis, FCD right temporal lobe	Scalp Sphenoid	Yes (Rt Monoplegia), poor neuropsychic development	Yes	Right temporal lobectomy	FCD Type Ia	24 months	Generalized Seizures 7-9 p/week	2/Pm	III
4	F	17	FCD of the left temporal lobe frontotemporal epilepsy	Scalp Sphenoid	No	No	Left anterior temporal lobectomy	FCD, Type Ic	60 months	Focal seizures 2-6 p/week	0-1 p/3 m	II
5	F	8	FCD inferior frontal gyrus.	Scalp (Fp1, F7, Fp2)	No	No	Frontal lobe lesionectomy	FCD, Type Ib	13 months	Focal seizures 8-11 p/week	0-1 p/3 m	II
6	F	2	FCD right temporal and right insular lobe	Scalp (T4, T6 Generalized discharges)	Poor neuropsychic development	Yes	Right anterior temporal lobectomy	FCD, Type Ic	36 months	Generalised seizures 3 p/day	0-1 p/3 m	II
7	M	12	Temporal lobe epilepsy, FCD The left temporal lobe	Scalp (T3, T5, F3, C3, P3)	Poor neuropsychic development	No	Left Anterior Temporal Lobectomy	FCD Type Ic	22 months	Focal Seizures. ≥3 p/d	0-1/Year	I
8	M	11	Leftl focal temporal lobe epilepsy. hippocampal sclerosis	Scalp (F7, T3, T5)	Yes	Yes	Left anterior temporal lobectomy	FCD Type Ia	30	Focal seizures ≥3 p/day	2/Pm	III
9	F	8	FCD Of The right frontal lobe	Scalp (Fp2, F4, F8)	Poor neuropsychic development	No	Frontal lobe lesionectomy	FCD Type Ib	15 months	Generalised seizures. ≥3 p/week	0-1 p/3 m	II
10	M	13	Right temporal lobe epilepsy	Scalp (F8, T4, T6)	Poor neuropsychic development deficit	No	RT temporal amygdalohippocampectomy	FCD Type Ib	18 months	Generalised Seizures ≥3 p/w	0-1 p/3 m	II
11	M	13	Right focal temporal lobe epilepsy	Scalp (C3, C4) Subdural (C4)	Kozhevnikov's syndrome	Right sided hemiparesis	Right temporal lobectomy	FCD Type Ic	11 months	Focal seizures ≥3 p/w	0-1 p/3 m	II

OND: Operative neurological deficit. F/P: Follow up period. FCD: Focal cortical dysplasias, EEG: Electro-encephalogram, Fp 1: Left pre-frontal lobe; Pre-OND Preoperative Neurological Deficit; Post-OND Postoperative Neurological Deficit; Seizures Post OT: Post operative treatment, Seizure type/rate Prior OT: Seizure type/rate Prior Operative time

**Table 2:** Anatomical location, Radiological and Ultrasound characteristics of lesion of individual patients. Intraoperative ultrasound (IoUS).

Patient #	Sex	Age	Anatomical location	MRI characteristic	IoUS characteristic	IoU prior resection lesión-brain interphase visibili prior resection	IoU post resection lesión residue
1	F	3 years	Frontal lobe	(MRI + VE)	**	Mildly clear	Present
2	F	12 years	Rt occipital lobe	(MRI + VE)	***	Clear	Present
3	M	35 years	Rt temporal Lobe	(MRI-VE)	*	Not clear	Non
4	F	17	Lt temporal Lobe	(MRI-VE)	**	Mildly clear	Non
5	F	8	Rt inferior frontal gyrus	(MRI + VE)	**	Mildly clear	Present
6	F	2	Lt temporal lobe	(MRI-VE)	**	Mildly clear	Non
7	M	12	Lt temporal lobe	(MRI + VE)	***	Clear	Non
8	M	11	Rt parietal Lobe	(MRI-VE)	*	Not clear	Present
9	F	8	Rt frontal Lobe	(MRI + VE)	**	Mildy clear	Present
10	M	13	Rt temporal lobe	(MRI + VE)	**	Mildly clear	Non
11	M	13	Lt temporal Lobe	(MRI-VE)	**	Mildly clear	Non

\*: Not visualized,\*\*: Poorly visualized blurry hyperechoic contours, \*\*\*: Clearly visualized blurry hyperechoic contours, MRI: Magnetic Resonance Imaging, IoUS: Intraoperative Ultrasound, Rt: Right, Lt: Left, IoU: Intraoperative Ultrasound

**Table 3:** MRI and IoUS signs and characteristics of FCD type I.

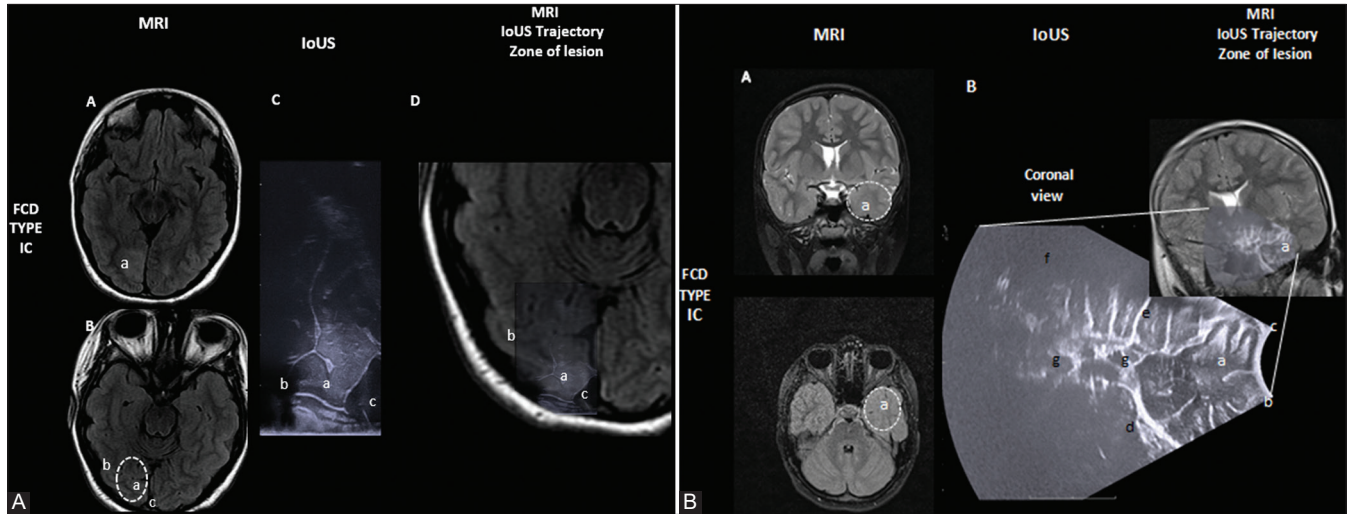
	Sign		Characteristics
	MRI	IoUS	
FCD Type Ia	1. Might present as an Isolated “Spark” Sign on MRI. Mostly presenting as “MRI negative”	1. Comparatively less visible to other Types of FCD 2. If visible: Nonspecific non-precise borders on MRI, T2WI and FLAIR which correspond on IoUS finding [Figure 1]	1. Lesion location is heavily dependent on clinical and EEG findings 2. Mostly affecting temporal lobe 3. Histological picture: Abnormal radial cortical lamination 4. Rare white matter involvement
FCD Type Ib	1. Light “Puff of smoke sign” on MRI	1. “Milky Way Sign” 2. Comparatively more visible to FCD Type Ia. Depicts more cortical hyper echogenicity on IoUS 3. Non -precise borders on MRI, T2WI and FLAIR .In tandem finding on IoUS	1. Lesion is located mostly out temporal lobe [Figure 2] 2. Histological picture: abnormal tangential cortical lamination
FCD Type Ic	1. “Fog sign” 2. Cortical thickening effacement of gray white matter junction, effacement of gyri and sulci	1. ” Thick smoke sign” 2. Comparatively more visible than FCD Type Ia and Ib. It depicts more cortical hyper echogenicity 3. Hyper-echoic in nature. Very similar to FCD Iia on IoUS. 4. Precise borders on MRI, T2WI and FLAIR, corresponding to IoUS	1. Mildly to rare white matter involvement 2. Affects any part of cerebral cortex 3. Histological picture: abnormal radial and tangential cortical lamination

FCD: Focal cortical dysplasias, EEG: Electro-encephalogram, FLAIR: Fluid attenuated inversion recovery, IoUS: Intraoperative ultrasound

was closely linked to depicted “EEG patterns” and in some circumstances with “MRI positive images.” Two patients, in whom FCD type Ic was histologically diagnosed, had clearly defined normal brain- lesion interphase. In these patients, there was a clear presence of increased cortical thickening and subcortical hyper intensity. Once the lesion was located, it was resected while real time sonography rechecks were conducted to reassess for residual tumor.

## DISCUSSION

To the best of our knowledge, at the time of writing, this is the first review describing IoUS features in FCD type I. Patients with FCD type I and its subtypes (types Ia, Ib and Ic) rarely exhibit frequent and severe seizure patterns in comparison to FCD types II and FCD types III.<sup>[13]</sup> Radical and safe removal of dysplastic brain tissue is an effective method of



**Figure 3:** A. FCD TYPE Ic A, B. MRI Flair in Axial view highlighting Rt Occipital FCD Type Ic (dashed lines). C, D; - depicting combined MRI and IoUS trajectory to the zone of FCD lesion with clearly visualized anatomical structures. a- FCD Type Ic; b - Rt Occipital lobe; c - Superior Sagittal Sinus. B. FCD TYPE Ic A;- MRI T2WI Coronal and MRI Flair Axial images depicting localization of Left temporal FCD Type Ic (dashed lines). B - highlighting coronal IoUS with combined coronal Mri and IoUS trajectory to the zone of FCD lesion clearly depicting adjacent anatomical structures; a - FCD Type Ic, b - left inferior temporal gyrus, c- middle temporal gyrus, d-cavernous sinus. g- internal carotid artery, e-internal capsule, f- third ventricle.

the treatment that achieves stable remission in patient with intractable epilepsy secondary to FCD type Ia.<sup>[8]</sup>

However, the MRI-negative FCD proportion of FCD type I is higher than MRI-positive FCD Type I.<sup>[12]</sup> This poses a considerable challenge for neurosurgeons (preoperative planning and intraoperative surgery) to appropriately appreciate MRI-negative FCD type I lesion location, and in the event located, demarcate brain-lesion junction. This is made especially difficult if the suspected lesion is within the vicinity of eloquent areas. Our experience in implementing IoUS during the resection of FCD type I is such that, taking note of the subtle sonographic (hyperechoic and hypoechoic) changes between normal and dysplastic tissue helped in achieving maximum yet safe resection. By depicting these subtle changes on MRI and IoUS, we developed, “Signs and Characteristics” to heighten suspicion of these lesions [Table 3] [Figures 1-3].

Commonly-encountered explanations for inadequate resection include: (1) inaccurate localization of diseased tissue and (2) brain shift that may happen at different stages during surgery – from the opening of dura mater, and potentially throughout the surgery – as tissue is resected. This often renders preoperative images inaccurate. Even intraoperative MRI could be not very useful, because it is a static image. Of the 11 patients with FCD, those particularly with histological type Ib and Ic had more lesion hyper echoic features which correspond to EEG focal epileptogenic interictal pattern.

In a study conducted by Tassi *et al.*, it was observed that patients with FCD I had a worse post-surgical seizure outcome.<sup>[13]</sup> In our patient group, the seizure preoperative rate ranged from more than 3–11 times/week. The frequency

of seizure rate was unrelated to anatomical location of the FCD (types Ia, Ib, and Ic). During the postoperative follow-up period, there was a considerable reduction in the seizure rates, most noticeably in patients with FCD type Ic – 72.7% of patients within a period of 1–5 years did not have disabling seizures (simple) to rare disabling seizures. This is most likely due to the ability to adequately visualize the offending lesion, its boundaries, and maximally resect it.

This study has not limitations since the study was carried out at a single center with the same team of neurosurgeons. We used the same intraoperative ultrasonography (iUS (FlexFocus 800 Ultrasound Machine BK Medical, Denmark) in all patients. This could offer some level of institutional bias. Second, the study had a small number of included patients to show significantly statistical analysis on the effectiveness of the application of IoUS. In the more optimistic future, it is hoped that a larger prospective study may be done to define the use of intraoperative ultrasound statistically adequately.

## CONCLUSION

IoUS is a useful aid in locating and delineating FCD type I lesions. With combinative preoperative EEG patterns (subdural grid and/or deep electrodes placements), recognizable “positive” or unrecognizable “negative” MRI, real-time IoUS, can enhance maximum “safe resection” epileptogenic foci.

## Declaration of patient consent

Patients’ consent not required as patients’ identities were not disclosed or compromised.

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**Conflicts of interest**

There are no conflicts of interest.

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