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Review Article

Evaluating intraoperative ultrasound (IOUS) in focal cortical dysplasia (FCD) resection surgery: A systematic review

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ABSTRACT

Background: Surgery is the best approach to treating focal cortical dysplasia (FCD)-related epilepsy; yet, it has suboptimal outcomes because distinguishing the boundaries between the FCD region and normal brain tissue intraoperatively poses a challenge. The use of intraoperative ultrasound (IOUS) helps demarcate FCD lesion borders leading to more accurate intraoperative resection. In this review, the use of IOUS for the resection of FCD was evaluated.

Methods: This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The Medline, Embase, Cochrane Library, Scopus Library, and Dynamed Library databases were searched, and two independent reviewers examined the articles. The search terms related to "drug-resistant epilepsy" and "intraoperative ultrasound." The results between January 2008 and April 2022 were abridged for FCD type, ultrasound resolution, extent of lesion resection, correction of brain shift, postoperative neurological deficits, and postoperative seizure freedom (Engel classification).

Results: Ten articles were included in the study. The parameters used to assess the efficacy of IOUS in FCD surgery were ultrasound resolution, demarcation of lesion boundaries, correction of brain shift, postoperative neurological deficits, and seizure freedom. Most studies have shown that IOUS produces high-resolution images. Surgery for Type 2 FCD patients had better outcomes than surgery for Type 1 FCD patients due to better visualization by IOUS. Patients were classified as Engel class 1 or class 2 postoperatively. Eight studies found that IOUS was superior to magnetic resonance imaging in brain shift correction.

Conclusion: The preliminary results look promising, especially for the international league against epilepsy class 2 FCD. However, there is a need for more high-quality research evaluating the use of IOUS in FCD and comparing it to other intraoperative imaging modalities.

Keywords: Drug-resistant epilepsy, Epilepsy surgery, Focal cortical dysplasia (FCD), Intraoperative ultrasound (IOUS)

INTRODUCTION

Epilepsy is a chronic, non-communicable neurological condition characterized by recurrent unprovoked seizures.[4,9] Approximately 55 million people are affected by epilepsy globally.[9] One-third of all affected individuals have drug-resistant epilepsy, whereby sufficient trials of two antiepileptic drugs have failed to control an individual's seizures, and 30–50% of drug-refractory epilepsy cases are accounted for by focal cortical dysplasia (FCD).[1,16] FCD is a malformation

of cortical development that arises as a result of both genetic and acquired factors.[11]

FCD was first described by Taylor *et al*. in 1971 as "congregations of large, bizarre neurons which were littered through all but the first cortical layer;"[24] its classification has since been modified on multiple occasions. A consensus was reached in 2011 to adopt the international league against epilepsy (ILAE) classification.[2,3] As its name suggests, FCD is a disease of the cerebral cortex. The cerebral cortex is composed of two areas: the 6-layered neocortex, which comprises 90% of the cerebral cortex, and the allocortex, which makes up only 10% of the cerebral cortex.[23] The ILAE classification is a three-tier classification system based on the lesion's histological findings. FCD type 1 is characterized by abnormal lamination (i.e., a blurred transition between different cortical layers) identified microscopically in the neocortex. Radial dyslamination is subclassified as type 1a, dyslamination in a tangential fashion is subclassified as type 1b and type 1c occurs when there is a combination of both radial and tangential dyslamination. FCD type 2 comprises dyslamination in addition to cytologic abnormalities. Type 2a occurs when neurons are dysmorphic, but balloon cells (neurons with a large cell body and opalescent glassy eosinophilic cytoplasm on H&E stain, lacking Nissl substance) are not observed. Type 2b is characterized by dysmorphia in the presence of balloon cells. FCD type 3 occurs when dyslamination is associated with another lesion, such as hippocampal sclerosis in type 3a, tumor in type 3b, and vascular malformations in type 3c. Type 3d occurs when any of these aforementioned lesions is acquired in early life.[3]

Since FCD-related epilepsy is typically of the drug-refractory type, surgery proves to be the best alternative currently, leading to postoperative seizure control in up to 80% of the patients if the lesion is completely resected.[21] Early promotion of the surgical option is of paramount importance in patients of the pediatric age group because uncontrolled epilepsy tends to cause developmental delay, behavioral disorders, and lower intelligence.[12,14] In addition, surgery has proven to be safer in those under the age of 18 than in adults.[12,14]

The most important prognostic factor of surgical outcome in FCD-related epilepsy patients is the completeness of lesion resection. [8] this is because the origin of the seizure is not necessarily the center of the lesion, but it could also arise from its periphery. Furthermore, the area of greatest cortical dysplasia does not necessarily correlate with the most epileptogenic area.[2] FCD lesion boundaries are very challenging to distinguish from normal brain tissue intraoperatively and sometimes exist in locations that are in close proximity to eloquent areas of the brain; this is likely a factor that contributes to increased surgical success rates when epilepsy is caused by non-FCD lesions such as tumors and cavernous hemangiomas.[25] Moreover, the spatial accuracy of neuronavigation, which is usually acquired from preoperative magnetic resonance imaging (MRI), is usually altered by brain shift upon manipulation of grid electrodes and cerebrospinal fluid loss, which occurs during surgery.[18]

Tools have been developed for intraoperative use to improve surgical outcomes for FCD. Imaging navigation systems with multiple fusion strategies, intraoperative MRI (IoMRI), and electrocorticography (ECoG), have proven very useful in facilitating the complete resection of FCD lesions, although they also come with inherent drawbacks.[12] ECoG produces recordings that are two-dimensional and only display functional (non-anatomical) properties of the lesion.[2] IoMRI has been successful in correcting brain shift but is still costly in terms of time and money; furthermore, it has a lower resolution than preoperative MRI because bleeding can cause artifacts. IoMRI requires enhanced surgical theatres and equipment and a long period of procedure interruption as the patient is moved in and out of the scanner.[17] In addition, it has been shown that dysplastic tissue can be more extensive than that seen on MRI, which is a major reason for poor surgical outcomes in FCD patients.[13]

Intraoperative ultrasound (IOUS), on the other hand, is easily accessible and inexpensive, allows real-time 3-dimensional visualization without the need for long periods of surgery interruption, clearly displays adjacent vasculature, allows postsurgical cavity exploration, and is very reliable in demarcating lesions borders even with FCD.[2,17,18] We searched the literature for the existence of a standard surgical technique for FCD resection, but none could be found. Then, we examined individual studies to determine how commonly IOUS was used in this type of surgery.[10,26] There are a few reports of IOUS in FCD surgery, and Zhao *et al*. reported the scarcity of research conducted in this area.[26]

Despite the reported poor success rate of FCD-related epilepsy surgery due to inadequate removal of the lesion as a consequence of unsatisfactory intraoperative imaging, only a few papers discuss ways to improve surgical technique and intraoperative imaging. Although IOUS is not a novel tool in neurosurgery and has proven beneficial in facilitating the resection of many brain lesions, such as tumors and arteriovenous malformations,[12] its potential with regard to assisting in FCD resection has not been adequately explored thus far.

This review was conducted to systematically review recent papers about the implications of using ultrasound intraoperatively to facilitate the resection of FCD lesions in terms of outcome, success rate, and seizure control, if proven beneficial, to encourage standardizing its utilization among all relevant centers. Furthermore, in this review, we examined the potential for future research in this area.

MATERIALS AND METHODS

The presented systematic review was conducted in adherence with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols 2020.[20] The papers included in the review specifically focused on the reliability of using IOUS in the complete resection of all types of FCD as classified by the ILAE in 2011.[3] This systematic review is registered in the PROSPERO register (ID: CRD42022367268).

Inclusion and exclusion criteria

The inclusion criteria were as follows: Articles published between January 2008 and April 2022 in the English language and involving at least one human participant (e.g., case report). Publications were excluded if they were not published with a full text (e.g., conference abstracts), involved only subjects with causes of epilepsy other than FCD (e.g., intra-axial solid tumors), involved the use of only non-IOUS imaging modalities**,** or had a surgical purpose that was not a laminectomy (e.g., depth electrode insertion).

Search strategy

The search for potentially relevant publications was employed on October 1, 2022, utilizing five bibliographic databases and registries (MEDLINE, EMBASE, COCHRANE, SCOPUS, and DYNAMED). Details of the MEDLINE and EMBASE search strategies are presented in Figures 1 and 2. The figures display the terms used to generate the reviewed papers and the way these terms were combined using "AND" and "OR" Boolean logic modifiers. Duplicates were eliminated, and the final search results were exported to Endnote. The SCOPUS and COCHRANE searches were conducted identically. DYNAMED was additionally screened to identify additional relevant references by reference searching the topic of "focal cortical dysplasia." The yielded publications were screened twice by two independent reviewers and were discussed until a consensus was reached. Had there been a persistent disagreement, the aid of a third reviewer would have been sought.

Data extraction and reporting

A table was created to chart the data. The data were abridged for the number of patients, type of FCD, ultrasound resolution, completion of lesion resection (postoperative MRI scans), mention of IOUS's value in the correction of brain shift, postoperative neurological deficits, and postoperative seizure freedom using the Engel classification system. To the best of our knowledge, no systematic reviews on this topic have been published. We intended to combine the data mentioned above for statistical analysis through a meta-analysis. However, due to the large heterogeneity of the data, a meta-analysis was found to be unsuitable, so we proceeded with a qualitative synthesis for the description of the data instead. Furthermore, a quantitative synthesis in the form of frequencies, percentages, and ranges was used to describe the cases of US-detected FCD and seizure freedom.

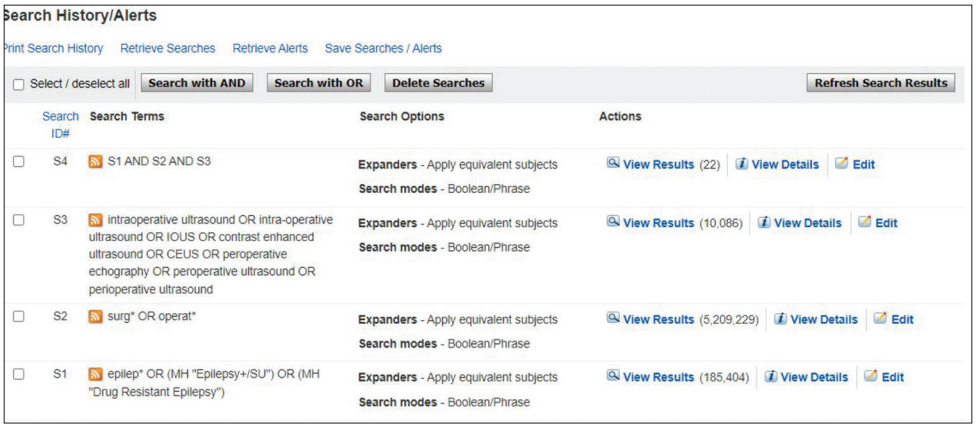

Figure 1: The MEDLINE search.

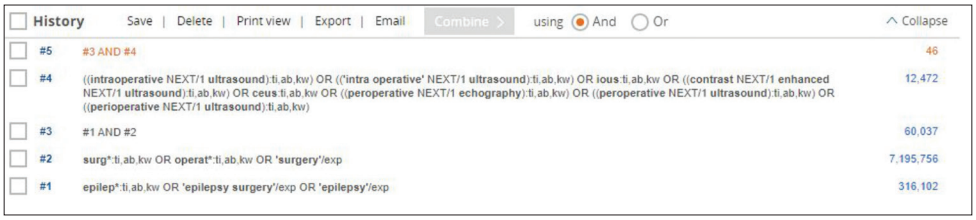

Figure 2: The EMBASE search.

Assessment of the quality of evidence

A total of ten studies were included in the study. Five studies had cohort designs, and the remaining five studies were case reports. The critical appraisal skills program (CASP) checklist for cohort studies was used to assess the risk of bias in the relevant studies[5] [Figure 3]. Two of the authors assessed the quality of the studies, and disagreements were resolved by discussion. The aid of a third party was not required to resolve the disagreement.

RESULTS

The databases employed for the search were MEDLINE, EMBASE, COCHRANE, SCOPUS, and DYNAMED, which yielded 22, 46, 20, 3, and 3 papers, respectively. Duplicates in the search, accounting for a total of 26 papers, were removed, leaving a remainder of 68 papers. The titles and abstracts of these 68 papers were read, and 36 irrelevant papers were excluded, along with a conference abstract for which a full text was not available.[7] The full-texts of the remaining 31 articles were then read and their references were searched to find other relevant studies. The original search already yielded all the relevant references. Of the full-text articles screened, 18 did not include patients with FCD and were thus excluded. Two additional papers were excluded because they did not mention the use of IOUS; rather, they focused on contrast-enhanced ultrasound. Papers published before the year 2008 (seven papers) and those that did not have full texts (i.e., conference abstracts) (one paper) were also excluded from the study. The remaining 11 articles were all relevant to the topic of interest and were found to be eligible for inclusion. However, two papers, Prada *et al*., 2019[22] and Prada *et al*., 2020 [22], were suspected of having involved the same cohort in both studies because the authors of both papers were the same, the patients recruited for the studies had undergone surgery during the same periods, and the patients also had the same FCD types. Therefore, Prada *et al*., in 2020 [22], have the paper chosen to be excluded because it involved a lower number of patients. Ultimately, ten papers in total were studied for this review [Figure 4].

Table 1 displays the selected studies for this review. A total of four papers were case reports; two were in a technical note format (one being a cohort study and the other a case report), and the rest were cohort studies. With regard to the cohort studies, the CASP checklist was used to determine the risk of bias.[5] The majority of the five cohort studies were found to have a low risk of bias [Figure 3].

The study with the largest number of patients was by Mathon *et al*.,[16] which involved 18 patients, followed by the Akeret *et al*. study[2], which involved 15 patients. In all studies, the patients were classified according to the ILAE classification except for the study by Mathon *et al*.[16] where they were classified according to the MRI status (i.e., visible on MRI or not). Six papers compared IOUS to other imaging techniques, such as preoperative MRI and shear wave elastography (SWE),[2,6,16-18,25] while the rest solely discussed IOUS and the postoperative outcomes of the patients. The parameters studied to evaluate the feasibility of IOUS in FCD surgery were ultrasound resolution, the ability to demarcate the lesion's boundaries, any reference of a benefit from correction of brain shift, the presence or absence of postoperative neurological deficits that manifest as motor deficits (paresis), sensory deficits or speech deficits,

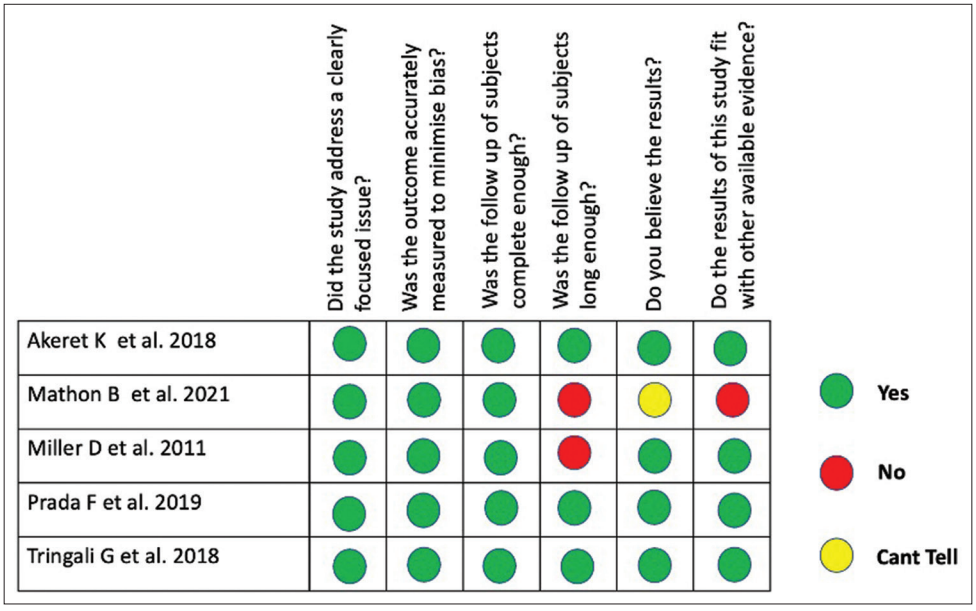

Figure 3: The critical appraisal skills program checklist.

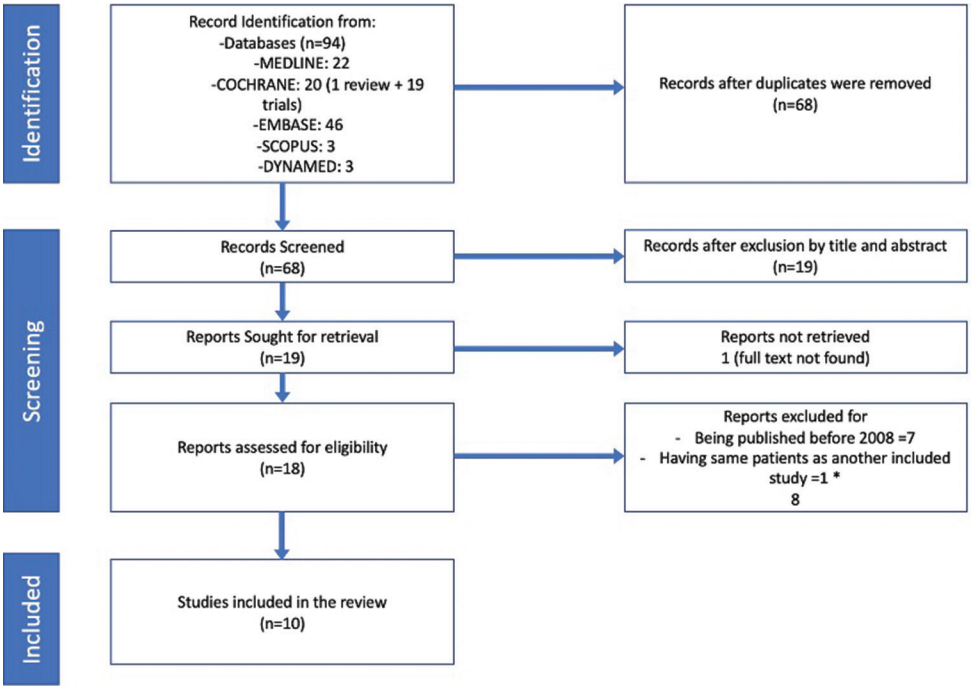

Figure 4: Preferred reporting items for systematic reviews and meta-analyses flow diagram. *n*: Number of papers, *: The excluded paper was titled "Intraoperative ultrasound techniques in focal cortical dysplasia surgery: A preliminary experience on a case series" (Prada *et al.*).

Table 1: Characteristics of the studies that were included in this review.

-	Authors, year	Study design	FCD types	Total cases	IOUS brand
1.	Miller *et al.*, 2008[18]	Case report	FCD 2b	1	NS
2.	Miller *et al.*, 2011[19]	Cohort	FCD 2b FCD 1	5	(Aplio, Toshiba, Japan) and (VectorVision2 with IgSonic-Integration, Brainlab, Germany; Sonowand, Trondheim, Norway)
3.	Chan *et al.*, 2014[6]	Case report	FCD 2b	1	Supersonic Imagine Aixplorer Ultrasound machine
4.	Lee *et al.*, 2014[12]	Case report	FCD 2a	1	(Esaote MyLab, Esaote, Italy)
5.	Akeret *et al.*, 2018[2]	Cohort	FCD 1 FCD 2	15	Philips iU22 Ultrasound machine
6.	Miller *et al.*, 2018[17]	Case report	FCD 2b	1	FlexFocus system (BK Ultrasound, Peabody, US)
7.	Tringali *et al.*, 2018[25]	Cohort	FCD 2b	6	(Esaote MyLab, Esaote, Italy)
8.	Prada *et al.*, 2019[21]	Cohort	FCD 2b	5	(MyLab Twice, Esaote, Italy)
9.	Martinoni *et al.*, 2021[15]	Case report	FCD 2b	1	Esaote MyLab Touch
10.	Mathon *et al.*, 2021[16]	Cohort	MRI negative and MRI positive	18	Supersonic Imagine Aixplorer Ultrasound machine

NS: Not specified, FCD: Focal cortical dysplasia, MRI: Magnetic resonance imaging, IOUS: Intraoperative ultrasound

and postoperative seizure freedom as described by the Engel classification.

All of the studied papers provided input on ultrasound resolution. The ability of the IOUS to demarcate the FCD boundaries was explained by eight of the ten studied papers. Similarly, eight of the ten papers referred to brain shift correction as a benefit of using IOUS. IOUS successfully detected 78–100% of FCD cases (42 out of a total of 54 patients). Furthermore, the US was superior to MRI in detecting FCD in 33–100% of cases. Postoperative outcomes were mostly explored through the Engel classification of seizure freedom as well as the ILAE classification. Most series reported good outcomes with Engel classes of 1 or 2 or ILAE classes of 1 or 2, reported to range between 56% and

100%. On the other hand, the occurrence of postoperative neurological deficits was mentioned in only six of the papers [Tables 1 and 2].

The IOUS transducer brand details were also documented, as was the expertise of the IOUS operator if mentioned by the author. The most commonly used IOUS machine brand was Esaote MyLab, a product from Italy that was used in at least three of the studies. Supersonic Imagine Aixplorer was the second most commonly used IOUS device brand and was used in the two studies that compared IOUS and SWE detection of FCD, as this device is capable of switching between standard B-mode ultrasound and SWE. Only one study did not specify the IOUS brand used.[18] Six of the ten papers acknowledged the clarity of the images produced by the IOUS and that their interpretation is heavily operator-dependent; however, only two papers described the qualifications of their IOUS operators. The IOUS operator in the Miller *et al*., (2018) study was, in fact, the first author himself, and he is stated to be a neurosurgeon trained in neurosurgical ultrasound.[17] Prada *et al*. relied on the consensus of two IOUS operators with >5 years of experience in ultrasound to interpret the IOUS images[21] [Tables 1 and 2].

Six articles compared traditional ultrasound (B-mode) imaging to other imaging techniques, such as ultrasound using SWE and MRI. Mathon *et al*. specifically examined the use of SWE in ultrasound imaging and compared it to the standard B-mode images routinely used in ultrasound. SWE allows the viscoelastic tissue characteristics to be analyzed, thereby distinguishing healthy brain tissue from aberrant tissue. It was found that SWE showed better detection of FCD compared to B-mode images, although the findings were not statistically significant (77.8% of cases were detected by SWE, and 11.1% of cases were detected by B-mode images, $P = 0.42$).[16] Similarly, a case report by Chan *et al*. also showed that SWE was successful in identifying an area of FCD that neither B-mode ultrasound nor MRI scans detected.[6] Meanwhile, two studies and two case reports compared the use of IOUS to MRI imaging. Akeret *et al*. reported that the visualization provided by IOUS was similar to that provided by preoperative MRI, while the resolution provided by IOUS was better than that provided by MRI imaging and allowed for better demarcation of FCD lesions and helped distinguish them from non-FCD lesions.[2,17,18,25] IOUS was also found to be superior to MRI in identifying the different subtypes of FCD.[2] Furthermore, as highlighted by Miller *et al*., IOUS has the advantages of lower costs and ease of access compared to other imaging modalities such as IoMRI.[17]

DISCUSSION

This systematic review identified ten publications that specifically addressed the use of IOUS in FCD surgery, published between the years 2008 and 2022. Publications regarding this specific topic are very scarce. There are no prior reviews that have addressed this topic.

Three factors were examined to measure the surgical success of IOUS-assisted FCD resection surgery: postoperative seizure freedom, neurological deficit, and postoperative MRI findings of residual FCD. Postoperative neurological deficit

Table 2: Overview of the literature on the results of using IOUS in patients with FCD.

Author, year	FCD types	US-detected FCD cases *n* (%)	Sonographer experience	US superior to MRI	Seizure-free outcomes *n* (%)	Total cases
Miller *et al*. 2008	FCD 2b	1 (100)	NS	NS	1/1 (100) Engel class IA	1
Miller *et al*. 2011	FCD 2b FCD 1	4/5 (80)	NS	4 (80)	1/5 (20) Engel class IB, 2/5 (40) Engel Class II	5
Chan *et al*., 2014	FCD 2b	1 (100)	NS	1 (100)	1/1 (100) ILAE class I	1
Lee *et al*. 2014	FCD 2a	1 (100)	NS	NS	1/1 (100) no seizures at 6 months	1
Akeret *et al*., 2018	FCD 1 FCD 2	15 (100)	NS	15 (100)	10/14 (71) Engel IA, 4/15 (27) Engel II	15
Miller *et al*., 2018	FCD 2b	1 (100)	US-trained neurosurgeon	1 (!00)	1/1 (100) Engel class IA	1
Tringali *et al*. 2018	FCD 2b	6 (100)	NS	6 (100)	5/6 cases (83.3) Engel class IA, 1/6 (17) Engel class IB	6
Prada *et al*. 2019	FCD 2b	5 (100)	2 observers with >5 years of US experience	3 (60)	1/5 (20) Engel Class IB, 4/5 (80) Engel Class IA	5
Martinoni *et al*., 2021	FCD 2b	1 (100)	NS	NS	NS	1
Mathon *et al*., 2021	NS	B-mode images: 2 (11); SWE: 14 (78)	NS	SWE superior in 6/18 (33)	1 year: 13 (72) ILAE class 1 or 2; last follow-up: 10 (56)	18

NS: Not specified, ILAE: International League against epilepsy, SWE: Shear-wave elastography, FCD: Focal cortical dysplasia, IOUS: Intraoperative ultrasound, MRI: Magnetic resonance imaging

is reflective of possible injury to an eloquent area of the brain, while the presence of residual FCD on postoperative MRI or incomplete postoperative seizure freedom status is indicative of incomplete FCD resection, which, as mentioned previously, is the most important factor for determining surgical success rates.[8]

A clear association can be seen between the type of FCD and the surgical success rate. Overall, surgery on FCD type 1 showed a less successful outcome than surgery on FCD type 2 patients. At least two of the papers included FCD type 1 patients.[2,19] Miller *et al*., (2018) study included one FCD type 1a patient and one FCD type 1b patient.[17] The FCD type 1a lesion was described to appear as "fair white hyperechogenicity" under IOUS, and the FCD type 1b lesion showed no change in echogenicity. Conversely, the remaining three cases, which were proven to have FCD type 2b by postoperative histology, were described to be "easily visualized," and their margins were clearly defined using IOUS. Nonetheless, postoperative MRI did not detect any residual FCD in any of the patients, and all had either an Engel class 1 or class 2 postoperatively. No mention of postoperative neurological deficits was made in their paper. The Akeret *et al*.[2] study shared almost identical views with the Miller *et al*. paper; it included one FCD type 1a patient, one FCD type 1b patient, one FCD type 1c patient, five FCD type 2a patients and six FCD type 2b patients. In this paper, all FCD cases were identifiable by IOUS, including the three FCD type 1 cases. However, as with the Miller *et al*. study,[17-19] it was difficult to precisely demarcate the lesion borders of the FCD type 1a and 1b cases, and postoperative MRI showed residual FCD in both cases. The FCD lesion in the type 1c patient was demarcated without difficulty, and the presence of residual FCD on postoperative MRI was "questionable." In all the FCD type 2 cases of this study, the sonographic abnormalities were more pronounced, and the IOUS more precisely delineated the borders. This resulted in postoperative MRI confirming a complete resection in all FCD type 2 cases. Fortunately, all patients in this study had a postoperative Engel class of either 1 or 2. As per the ILAE classification of FCD, the more prominent the histological abnormalities of the FCD are, the greater the ILAE class. Type 1 lesions are histologically more subtle than type 2 lesions and, therefore, are less prominent on IOUS.

The majority of the selected papers commended the use of IOUS in this kind of surgery, particularly for type 2 FCD lesions. Eight studies expressed appreciation of the fact that IOUS corrected brain shift as opposed to the standard neuronavigation system that is built from preoperative MRIs. Specific praise was also shown for the high resolution of the IOUS; in fact, two of the papers declared IOUS's resolution superior to that of preoperative MRI.[2,21] Two of the papers did not make mention of IOUS resolution because their main focus was on SWE. The ability of IOUS to demarcate FCD borders among different papers was brought to attention, and it specifically showed greater precision with FCD type 2. However, one of the papers reported that an FCD 2b lesion was completely undetectable by IOUS but was easily picked up on SWE.[6] Although this paper revealed that IOUS is highly operator-dependent, it made no mention of the operator's experience and qualifications. In addition, as previously mentioned, the IOUS brand likely plays a role in the effectiveness of resection; however, both operator experience and the IOUS brand cannot be evaluated, as this study was a case report involving only one patient.

The foremost limitation of this study is that the topic is rare and has not been studied extensively. Only ten papers met the inclusion criteria of this review; all involved a very small sample size, none were comparative prospective studies, and only two of the papers denied any external funding. Although the results look very promising and show impressive outcomes when using IOUS to assist in FCD resection surgery, it is difficult to draw a firm conclusion considering the limitations mentioned above. The data in the chosen studies additionally showed considerable heterogeneity, thus preventing us from conducting the initially intended meta-analysis. Therefore, we strongly encourage institutions to conduct high-quality comparative, prospective studies that standardize dependent variables such as operator expertise and IOUS brand. Further, research in this direction has the potential to improve the quality of life in many seizure patients.

CONCLUSION

The best treatment modality currently available for drug-refractory patients to improve their quality of life is epilepsy surgery. FCD patients make up 30–50% of all drug-refractory epilepsy cases, and surgery in FCD cases had the least favorable outcome among all other causes of drug-refractory epilepsy. This is a result of the difficulty in distinguishing dysplastic from normal tissue intraoperatively, which is extremely influential because the completeness of resection of the lesion is the most important predictor of the surgical outcome. Unfortunately, studies conducted to seek improvement in intraoperative imaging for this lesion are very sparse. The objective of this paper was to explore the potential of IOUS to improve the outcome of this form of surgery by systematically identifying and critiquing as many relevant papers as possible. This review highlights the potential value of IOUS, especially for ILAE class 2 FCD, which shows potentially better outcomes than those of other modalities such as IoMRI, SWE, and ECoG. Furthermore, this review identified a gap in the literature and highlighted that more high-quality comparative research in this area is warranted, with particular emphasis on ILAE class 1 FCD.

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Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent was not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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