Received: 6 December 2022 | Revised: 3 August 2023 | Accepted: 4 August 2023

DOI: 10.1111/epi.17739

Epilepsia™

RESEARCH ARTICLE

Stereoelectroencephalography-guided laser ablation in neocortical epilepsy: Electrophysiological correlations and outcome

Thandar Aung[1,2] | **Olesya Grinenko**[1,3] | **Jian Li**[4,5] | **John C. Mosher**[6] | **Patrick Chauvel**[1,2] | **Jorge Gonzalez-Martinez**[1,2,7]

[1]Department of Neurology, Epilepsy Center, Cleveland Clinic, Ohio, Cleveland, USA

[2]Department of Neurology, Epilepsy Center, University of Pittsburgh Medical Center, Pennsylvania, Pittsburgh, USA

[3]Mercy Health Grand Rapids Medical Education, Michigan, Grand Rapids, USA

[4]Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital and Harvard Medical School, Massachusetts, Charlestown, USA

[5]Department of Neurology, Center for Neurotechnology and Neurorecovery, Massachusetts General Hospital and Harvard Medical School, Massachusetts, Boston, USA

[6]Department of Neurology, Texas Institute for Restorative Neurotechnologies, McGovern Medical School, University of Texas Health Science Center at Houston, Texas, Houston, USA

[7]Department of Neurosurgery, Epilepsy Center, University of Pittsburgh Medical Center, Pennsylvania, Pittsburgh, USA

Correspondence
Thandar Aung, Department of Neurology, Epilepsy Center, University of Pittsburgh Medical Center, 3471 Fifth Avenue, Pittsburgh, PA 15213, USA.
Email: aung.thandar@outlook.com

Abstract

Objective: We aimed to study the correlation between seizure outcomes in patients with drug-resistant epilepsy (DRE) who underwent laser interstitial thermal therapy (LITT) and stereoelectroencephalographic electrophysiologic patterns with respect to the extent of laser ablation.

Methods: We retrospectively analyzed 16 consecutive DRE patients who underwent LITT. A seizure onset zone (SOZ) was obtained from multidisciplinary patient management conferences and again was confirmed independently by two epileptologists based on conventional analysis. SOZs were retrospectively divided into localized, lobar and multilobar, and nonlocalized onset types. A posteriori-predicted epileptogenic zone (PEZ) was identified using the previously developed "EZ fingerprint" pipeline. The completeness of the SOZ and PEZ ablation was compared and correlated with the duration of seizure freedom (SF).

Results: Of 16 patients, 11 had an a posteriori-identified PEZ. Three patients underwent complete ablation of SOZ with curative intent, and the other 13 with palliative intent. Of three patients with complete ablation of the SOZ, two had concordant PEZ and SOZ and achieved 40- and 46-month SF without seizure recurrence. The remaining patient, without any PEZ identified, had seizure recurrence within 1 month. Six of 13 patients with partial ablation of the SOZ and PEZ achieved mean seizure freedom of 19.8 months (range = 1–44) with subsequent seizure recurrence. The remaining seven patients had partial ablation of the SOZ without the PEZ identified or ablation outside the PEZ with seizure recurrence within 1–2 months, except one patient who had 40-month seizure freedom after ablation of periventricular heterotopia.

Significance: Only complete ablation of the well-restricted SOZ concordant with the PEZ was associated with long-term SF, whereas partial ablation of the PEZ might lead to SF with eventual seizure recurrence. Failure to identify PEZ and ablation limited to the SOZ often led to 1–2 months of SF.

Thandar Aung and Olesya Grinenko are co-primary authors and contributed equally to the paper.

KEYWORDS
drug-resistant, epilepsy, epilepsy surgery, laser ablation, EZ fingerprint

1 | INTRODUCTION

Laser interstitial thermal therapy (LITT) has been used to treat brain neoplasms over the past 4 decades.[1] With technical advances in probe design, assisted stereotaxy, and intraoperative magnetic resonance imaging (MRI) thermography, LITT is now considered an emerging, less-invasive technique for brain neoplasms and epilepsy, and an alternative to craniotomy-based resections.[2] The efficacy of LITT in epileptic patients, in either lesional or nonlesional scenarios, is variable among different studies. MRI-visible lesions and mesial temporal sclerosis are important variables predicting seizure freedom following the LITT, but the seizure recurrence rate seems to increase over time.[3–11] As MRI-visible lesions may or may not overlap with the epileptogenic zone (EZ), "lesion-based" treatment modalities are frequently associated with unfavorable seizure outcomes in both LITT and open procedures.[12–16] To address the challenges in highly selective procedures, stereoelectroencephalography (SEEG) can be applied to delineate EZ and guide LITT.[8,15] As the anatomical reach of ablation effect from the current LITT systems is restricted up to approximately 1 cm radius from the center of the probe, LITT might be ideal for well-defined and restricted EZ, perhaps in cases where the EZ and the seizure onset zones (SOZs) are anatomically overlapping.[3,17–20] To date, no consensus on SEEG electrophysiologic patterns has been reported that would precisely identify EZ to guide and predict seizure outcomes after LITT. An EZ electrophysiologic biomarker, "EZ fingerprint," has been recently described using time-frequency (TF) analysis and validated in focal epilepsies.[21,22] The pattern is characterized by three elements identified during the period of preictal to ictal transition: preictal spikes, narrow-band fast activity (FA), and concurrent low-frequency suppression.[21,22]

Herein, we studied a series of patients with drug-resistant epilepsy (DRE) who underwent SEEG-guided LITT to compare and correlate the seizure outcome with ablation of the SOZ based on conventional analysis. Then, we correlated the seizure outcome with the ablation of a posteriori-identified EZ using the previously developed "EZ fingerprint" pipeline.[21,22] Identified EZ contacts from the pipeline were named the predicted epileptogenic zone (PEZ).

Key Points

- Compared to resective epilepsy surgery, LITT is intended to be a less invasive treatment method for medically refractory epilepsy, but its long-term efficacy still requires validation
- Our study describes long-term seizure outcomes of SEEG-guided LITT with respect to the intracranial electrographic characteristics of the EZ
- We demonstrate the value of the "EZ fingerprint" biomarker in identifying optimal targets and candidates for SEEG-guided LITT in medically refractory neocortical epilepsy

2 | MATERIALS AND METHODS

2.1 | Patient selection and data collections

This retrospective study was conducted under the approval of the institutional review board of Cleveland Clinic. Patients with focal DREs who underwent SEEG extraoperative explorations and SEEG-guided LITT between June 2013 and July 2015 were consecutively enrolled. A total of 17 patients were identified and included in our initial cohort. The inclusion criteria were: (1) patient underwent SEEG-guided LITT, (2) one or more seizures were recorded during the SEEG, and (3) there was at least 1-year follow-up after the laser ablation. From the cohort of 17 patients, one patient did not have a habitual seizure during the SEEG evaluation and was excluded. We collected retrospective data from medical records: age at onset; epilepsy duration; localization and type of lesion based on the MRI; report of multidisciplinary patient management conference (PMC) with SOZ, indication for LITT, and ablation details (i.e., exact electrode contacts and targets); seizure frequency before and after LITT; duration of follow-up; and duration of seizure freedom. Seizure outcome was defined based on the duration of seizure freedom. Time to seizure recurrence was used to calculate the duration of seizure freedom.

All patients underwent preoperative evaluation, including scalp video-EEG monitoring, MRI, positron emission

tomography, ictal single photon emission computed tomography, and neuropsychological assessment. Due to the incongruent noninvasive preoperative data, recommendations for extraoperative invasive monitoring with SEEG methodology were made during a multidisciplinary PMC, including neurologists, neurosurgeons, neuroradiologists, and psychologists. SEEG electrodes (DIXI Medical) were implanted according to the preimplantation hypotheses using the Talairach stereotaxic method.[23] SEEG signals were recorded using a Nihon Kohden EEG machine with a sampling rate of 1000 Hz. The mean number of electrodes per patient was 12.3 (range = 7–17), with bilateral implantation in seven patients.

Anatomical locations of the electrode contacts were identified by a digital fusion of postimplantation thin-sliced computed tomographic (CT) image with the preoperative T1-weighted MRI using CURRY 7 (Compumedics NeuroScan). Postoperative T1-weighted MRI was then coregistered to the postimplantation CT image to identify the position of the electrode contacts with respect to the location of LITT-ablated contacts.

After the SEEG evaluation, each patient's case was discussed in a second multidisciplinary PMC. Based on the full set of clinical data, including the SOZ, seizure semiology, and MRI lesion, the option of SEEG-guided LITT was offered if (1) the EZ was restricted and refined to a limited region and (2) complete resection of the EZ was not feasible due to overlapped functional cortex and/or bilateral/multifocal hemispheric location with the expectation of a reduction in the seizure frequency and/or severity.

Patients underwent the SEEG-guided LITT approximately 6 weeks following the removal of the SEEG electrodes. The SEEG-guided LITT was planned according to the SOZ contacts identified in the PMC. The SEEG-guided LITT was performed in an intraoperative MRI suite under robotic guidance. The robotic assistant device, containing the patient's previous SEEG plan and, consequently, the selected trajectories and SOZ targets to be treated (based on the PMC consensus), was used to precisely guide the laser ablations using the laser applicators (Monteris Medical; Visualase). Techniques and concepts related to the SEEG-guided LITT were previously described by our group.[8]

2.2 | Definition and calculation of ablation volumes

The ablation volumes for each patient were digitally calculated from the postoperative contrasted volumetric MRI sequences, which were performed 24 h after the ablative procedure. The images for each subject were loaded into commercially available surgical planning software (iPlan Cranial 3.0, Brainlab). The ablation-created cavity borders were manually outlined, and subsequently, the software calculated the volume of the definitive ablation cavity. The applied software tool used a semiautomatic voxel-based segmentation method to calculate the treated volume (Figure 1).

2.3 | Data selection, TF decomposition, identification of PEZ, and classification of SOZ

SEEG data obtained from patients who underwent LITT were retrospectively analyzed to identify the PEZ. All recorded seizures with sustained FA at seizure onset were included in the analysis.[21] If no sustained FA was observed at seizure onset, "EZ fingerprint" analysis was not performed. For each seizure, 40 s of SEEG data were extracted, with 20 s before the seizure onset and 20 s after. To establish the baseline, we extracted 40 s of SEEG data 2 min before seizure onset. Both the ictal and baseline SEEG data were transformed into the TF maps using Morlet wavelet transform (using central frequency of 1 Hz, time resolution of 3 s). The seizure TF maps were then normalized against the baseline maps for each frequency. All the analyses were performed in a bipolar montage where the differences between pairs of adjacent contacts on each electrode were computed. For artifact reduction, complex independent component analysis was used to identify and remove artifacts that were common across all channels (i.e., powerline). In addition, channels containing obvious artifacts were identified and removed (i.e., contacts outside the brain or in the ventricles). None of the channels around the SOZ was removed. The "artifact-free" normalized TF maps were then used to extract three distinct features: preictal spikes, FA, and suppression of low-frequency activity.

Finally, we used the support vector machine (SVM) classifier trained on a set of seizure-free patients in our previous study,[21] and a prediction was made for each contact in each seizure. The predicted electrode contacts were identified as the PEZ. In this group, PEZ across multiple seizures were mostly consistent across multiple seizures. If predicted contacts varied across the seizures in one subject, all predicted contacts from all patients' seizures were included in the PEZ. Further details on the "EZ fingerprint" pipeline were fully described in previously published articles and their supporting documents.[21,22,24]

Data on each patient's SOZ were obtained retrospectively from the multidisciplinary PMC, which occurred after the SEEG evaluation was completed (as described in Section 2.1). Two epileptologists (T.A. and O.G.) then retrospectively confirmed the localization of the SOZ by

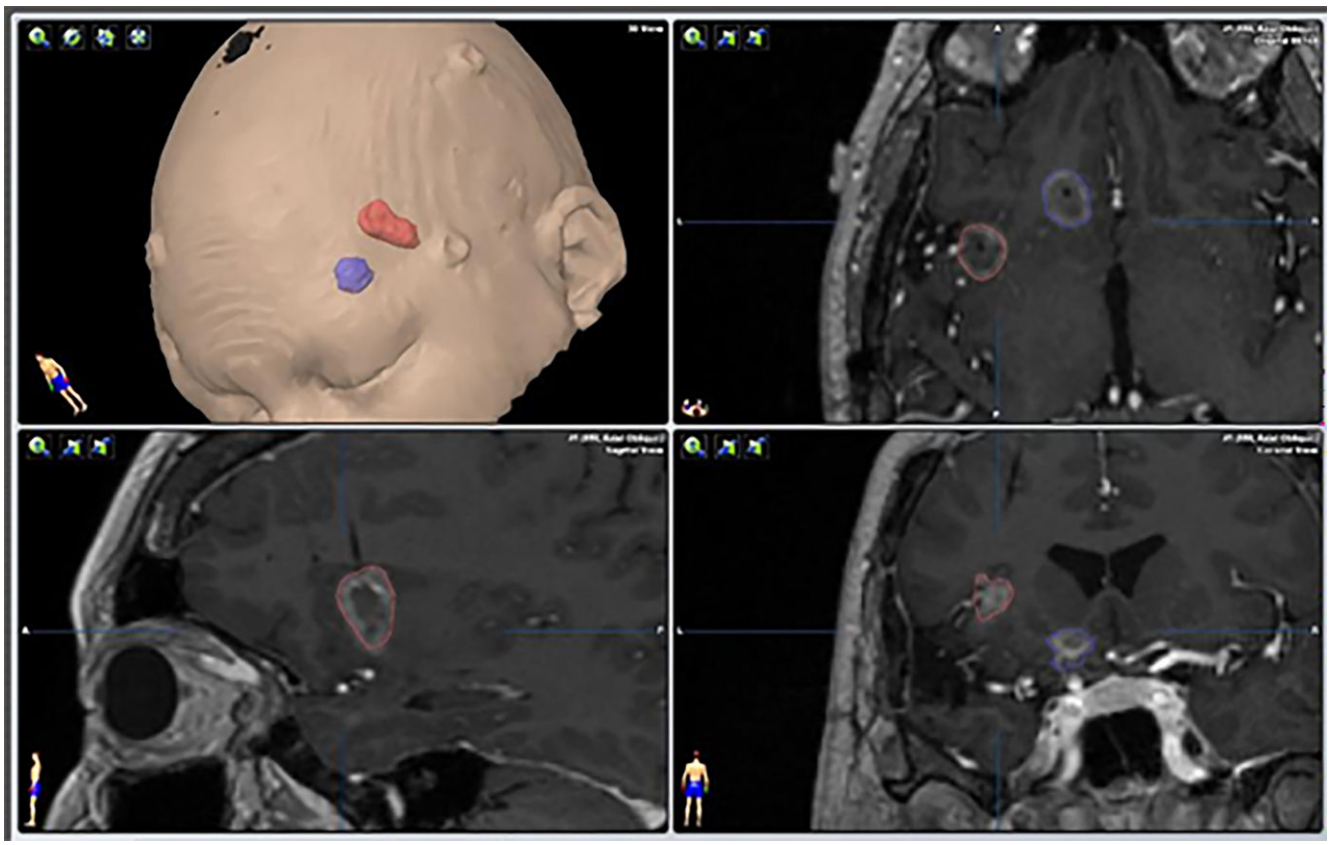


FIGURE 1 Calculation of ablation volume of Subject 9. The volumes were digitally calculated from the postoperative contrasted volumetric magnetic resonance imaging sequences in three different orientations (axial, sagittal, and coronal) using the volume tool from the surgical planning software tool kit (iPlan Cranial 3.0, Brainlab). The superior left panel depicts two volumetric areas corresponding to the ablation of two seizure onset zone contacts.

conventional visual analysis without knowing the data on the PEZ. We then subdivided SOZ into two major groups: localized (either lobar or multilobar) and nonlocalized. Localized SOZ type was defined when the SOZ had a restricted location with clear boundaries (1) in adjacent depth electrode contacts within one lobe, including perirolandic and insulo-opercular areas (localized lobar SOZ; Figure 2A); or (2) within two or more lobar regions (localized multilobar SOZ). Nonlocalized onset was defined as when the SOZ involved multiple electrodes over noncontinuous, multiple lobes without clear boundaries (Figure 2B).

The SOZ and PEZ electrode contacts were identified independently. Subsequently, we manually quantified the anatomical relationship between the contacts containing the PEZ, the SOZ, and the laser-ablated regions, determining whether the PEZ and SOZ were fully ablated, partially ablated, or not ablated. We compared the completeness of ablation of the PEZ and SOZ with the duration of seizure freedom and outcome at the last follow-up visit.

3 | RESULTS

3.1 | Study participants and demographics, regions of LITT, and ablation volumes

A total of 16 patients were included in the study (Table 1). The average age at the evaluation for epilepsy surgery was 29.6 years (range = 19–53), with an average follow-up period of 44 months (range = 21–79). The average age of epilepsy onset was 12 years (range = 0–35). Only two patients (12.5%) had lesional MRI (polymicrogyria and periventricular heterotopia [PVH]). Regarding the location of LITT, the majority of patients (56%, $n = 9$) underwent ablation in insulo-opercular regions. Seven patients had ablation only in insulo-opercular regions, and two had ablation in both insulo-opercular and frontal regions. The mean ablation volume for the respective treated targets was 2.59 mL (median = 2.48, range = .93–6.7). No complication related to the SEEG or LITT was noted in this cohort.

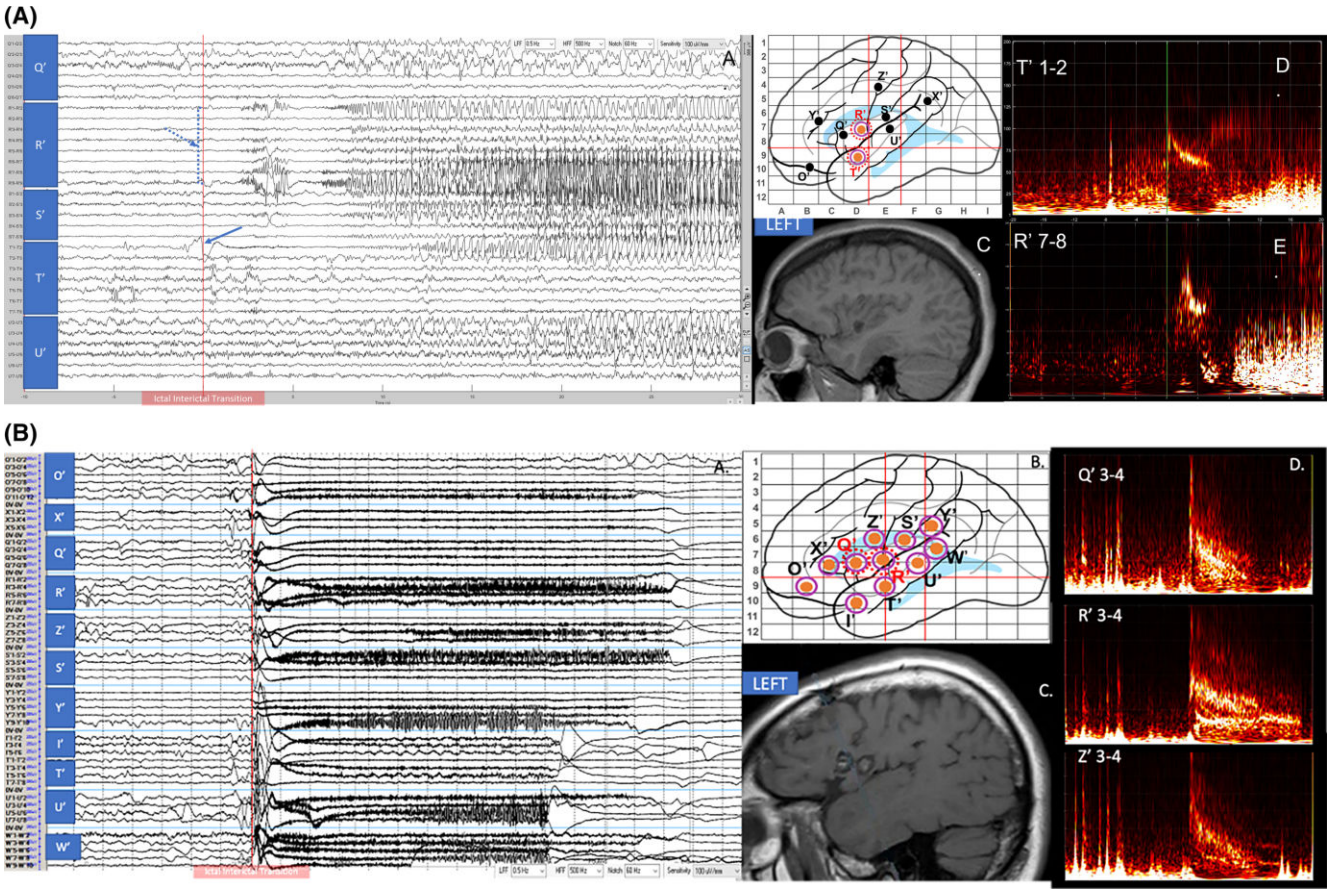


FIGURE 2 (A) Localized lobar seizure onset zone (SOZ) in insulo-opercular regions for Subject 2. (a) Stereoelectroencephalography (SEEG) time series illustrating localized SOZ. Low-voltage fast activity associated with suppression and preictal spikes is seen over the T′ 1–2 (blue arrow) and R′ 1–9 contacts (dotted blue arrow). (b) Implantation map with marked electrodes, which includes the predicted epileptogenic zone (PEZ; orange color), SOZ (purple circle), and laser-ablated contacts (red labeled electrodes and red dotted circles). (c) Postoperative magnetic resonance imaging (MRI) illustrating ablation of T′ 1–2 contacts and R′ 1–9 contacts. (d, e) Time-frequency plot of interictal to ictal transition in T′ 1–2 contacts and R′ 7–8 contacts illustrating "EZ fingerprint" pattern (identified as PEZ), which includes fast activity at seizure onset and associated suppression of low frequencies (with preictal spiking in the T'1-2 contacts). (B) Nonlocalized SOZ for Subject 12. (a) SEEG time series illustrating nonlocalized SOZ. Synchronous low-voltage fast activity is seen over almost all electrode contacts at seizure onset. (b) Implantation map with marked PEZ, SOZ, and laser-ablated electrodes. (c) Postoperative MRI illustrating ablation of Q′ 1–8 and R′ 2–9 contacts. (d) Time-frequency plot of interictal to ictal transition in Q′ 3–4 and R′ 3–4 and Z′ 3–4 contacts illustrating the "EZ fingerprint" pattern (identified as PEZ), which includes preictal spiking activity, fast activity at the seizure onset, and associated suppression of low frequencies.

3.2 | Correlation of seizure outcome with type of SOZ and completeness of SOZ and PEZ ablation

In our retrospective study of 16 patients, 11 were identified as localized SOZ (four with localized lobar and seven with localized multilobar SOZ). The remaining five patients had nonlocalized SOZ. Retrospectively, "EZ fingerprint" analysis was performed on patients with FA at seizure onset (13/16 patients), and a total of 57 seizures were analyzed. From this analysis, 11 of 13 patients had a PEZ.

Only three patients underwent LITT with the intent of complete ablation of the SOZ. The remaining 13 patients underwent LITT with the intent of palliative treatment with partial SOZ ablation due to the multifocal or nonlocalized SOZ (Table 2). Details of the anatomical location of the SOZ, PEZ, and ablation area are presented in Table 3.

3.2.1 | Seizure outcome in patients with complete ablation of SOZ

Subjects 1, 2, and 3 had volumetrically restricted localized lobar SOZ (Tables 2 and 3). In Subjects 1 and 2, the PEZ overlapped the SOZ, and both were completely

TABLE 1 Demographic details of patients who underwent LITT.

Characteristic	Total patients, $N=16$
Age at evaluation, years, mean ± SD (range)	29.6 ± 9.7 (19–53)
Age of epilepsy onset, years, mean ± SD (range)	12 ± 11.8 (0–35)
Male, *n* (%)	11 (69%)
Implantation scheme	
Unilateral, *n* (%)	9 (56%)
Left, *n*	7/9
Right, *n*	2/9
Bilateral, *n* (%)	7 (44%)
Lesion, *n* (%)	2 (12.5%)
Lobar regions of LITT, *n*	
Insulo-operculum	7
Insulo-operculum and frontal	2
Frontal	3
Parietal	2
PVH	1
Questionable periventricular lesion	1
Laser trajectories, *n*	25
Regions of ablation [of 25 trajectories], *n*	
Frontal	5
Insulo-operculum	13
PVH	1
Parietal	2
Precentral gyrus [central lobules]	1
Temporal [posterior superior temporal sulcus]	2
Questionable periventricular lesion	1
Side of ablation, *n* (%)	
Right	8 (50%)
Left	8 (50%)
Seizure-free patients at the last follow-up visit, *n* (duration of SF)	2 (40 and 46 months)
Ablation volume, mL, mean (range)	2.59 (.93–6.7)
Duration of follow-up, months, mean ± SD (range)	44 ± 13 (21–79)

Abbreviations: LITT, laser interstitial thermal therapy; PVH, periventricular heterotopia; SF, seizure freedom.

ablated. Both patients were seizure-free at the last follow-up visit at 40 and 46 months, respectively. Subject 3 had complete ablation of the SOZ without any PEZ identified (due to no FA at seizure onset), and seizure recurred within 1 month.

3.2.2 | Seizure outcome in patients with partial ablation of SOZ

Six patients (Subjects 4, 5, 6, 9, 11, 12) with partial ablation of the SOZ and PEZ (one with localized lobar, four with localized multilobar, and one with nonlocalized) achieved a mean seizure freedom of 19.8 months (range = 1–44) with subsequent seizure recurrence (Tables 2 and 3). Subject 4, with the localized lobar SOZ, had overlapped PEZ and SOZ identified in contacts in close vicinity. The SOZ and PEZ were partially ablated. The patient had temporary seizure control, with seizure recurrence 16 months after LITT. Similarly, two patients (Subjects 9 and 11) with localized multilobar SOZ had colocalized SOZ and PEZ over the same regions, which were partially ablated (Table 3). They achieved long-term seizure freedom of 42 and 44 months, respectively, with subsequent seizure recurrence. The remaining two patients (Subjects 5 and 6) with localized multilobar SOZ had only partially overlapped SOZ and PEZ in the distant regions (Table 3). The patients had seizure recurrence after 9 and 1 month, respectively. Subject 12 had nonlocalized SOZ and lesional MRI (polymicrogyria). Multiple PEZs were predicted diffusely over the multiple electrodes, and only two lesional PEZ electrodes were in the laser-ablated area. The patient achieved 7-month seizure freedom.

Seven patients (Subjects 7, 8, 10, 13, 14, 15, 16) had partial ablation of the SOZ without any PEZ identified or ablation outside the PEZ, and the majority of these patients had seizure recurrence within 1 or 2 months (Tables 2 and 3). Three patients (Subjects 7, 8, 10) had localized multilobar SOZ, and four (Subjects 13, 14, 15, 16) had nonlocalized SOZ. The PEZ was identified in three patients (Subjects 7, 13, 14). In Subjects 7 and 14, although the SOZ was partially ablated, none of the PEZ contacts was part of the ablation (Table 3). The patients had seizure recurrence within 1 month after LITT. In Subject 13, PVH was identified on MRI and was targeted by LITT. Even though the PEZ was identified over the posterior perisylvian cortex and was not part of the ablation, the patient achieved 40 months of seizure freedom, with subsequent seizure recurrence. The remaining patients had no PEZ identified. Subjects 8, 10, 15, and 16 had seizure recurrence within 1 or 2 months after the procedure. Despite early recurrence, Subject 10 achieved subsequent seizure freedom on antiseizure medication at 40-month follow-up (Table 2).

These findings suggest that complete or substantial ablation of both the SOZ and PEZ resulted in longer seizure freedom periods, whereas partial or nonoverlapping ablation of the SOZ and PEZ correlated with early seizure recurrence.

TABLE 2 Type of SOZ, MRI findings, intent of LITT, completeness of ablation of SOZ and PEZ, and seizure outcome.

Subject	Type of SOZ	MRI finding	Intent of LITT/ablation of SOZ	Ablation of PEZ	Duration of SF
1	Localized lobar (frontal)	Neg	Curative/complete	Complete	No SZ recurrence/46-month SF
2	Localized lobar (insulo-opercular)	Neg	Curative/complete	Complete	No SZ recurrence/40-month SF
3	Localized lobar (parietal)	Neg	Curative/complete	None predicted[a]	1-month SF
4	Localized lobar (frontal)	Neg	Palliative/partial	Incomplete	16-month SF
5	Localized multilobar (frontoparietoinsulo-opercular)	Neg	Palliative/partial	Incomplete	9-month SF
6	Localized multilobar (frontoinsulo-opercular)	Neg	Palliative/partial	Incomplete	1-month SF
7	Localized multilobar (perirolandic–insulo-opercular)	Neg	Palliative/partial	Ablation outside PEZ	1-month SF
8	Localized multilobar (frontoinsular)	Neg	Palliative/partial	None predicted[a]	2-month SF
9	Localized multilobar (frontoinsulo-opercular)	Neg	Palliative/partial	Incomplete	42-month SF
10	Localized multilobar (temporoinsulo-opercular)	Neg	Palliative/partial	None predicted	SZ recurrence in 1 month followed by 40-month SF
11	Localized multilobar (bilateral insulo-opercular)	Neg	Palliative/partial	Incomplete	44-month SF
12	Nonlocalized	Polymicrogyria	Palliative/partial	Incomplete	7-month SF
13	Nonlocalized	PVH	Palliative/partial (targeted PVH)	Ablation outside PEZ	40-month SF
14	Nonlocalized	Neg	Palliative/partial	Ablation outside PEZ	1-month SF
15	Nonlocalized	Neg	Palliative/partial	None predicted	1-month SF
16	Nonlocalized	Neg	Palliative/partial	None predicted[a]	1-month SF

Abbreviations: LITT, laser interstitial thermal therapy; MRI, magnetic resonance imaging; Neg, negative; PEZ, predicted epileptogenic zone (a posteriori-identified epileptogenic zone contacts using the "EZ fingerprint" pipeline); PVH, periventricular nodular heterotopia; SF, seizure freedom; SOZ, seizure onset zone; SZ, seizure.

[a]No fast activity at seizure onset.

TABLE 3 Illustration of the detailed anatomical location of SOZ (purple circles), PEZ (orange electrodes), and ablated contact (red labeled electrode names with red dotted circles), with seizure outcome.

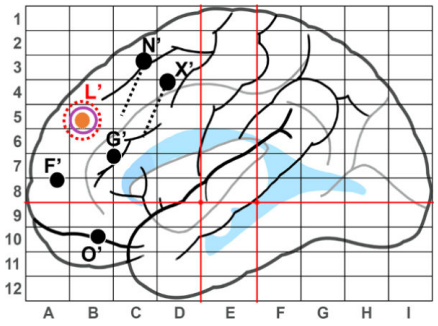
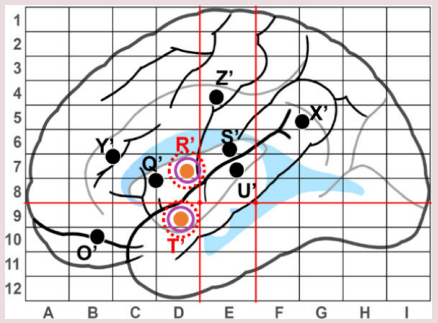
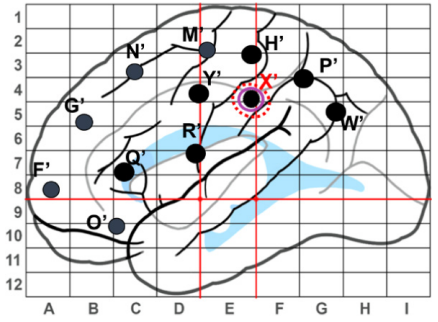
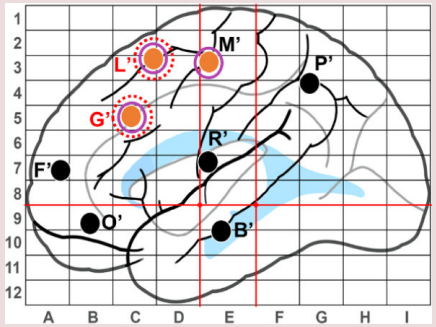
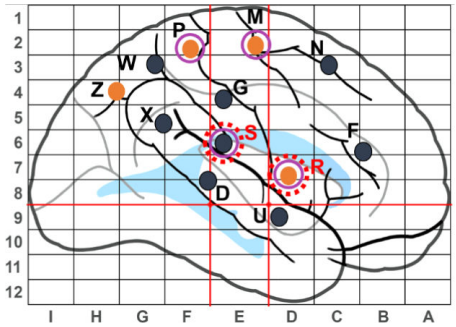
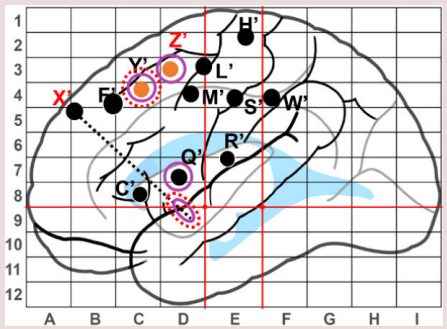
Subject	Implantation map	SOZ electrode contacts	A posteriori-identified PEZ electrode contacts	Laser-ablated electrode contacts	SF/NSF
1		L' 1-6 (mesial frontal cortex)	L′ 1–6 = SOZ	L′ 1–6 = SOZ	SF (46-month follow-up)
2		R' 1-9 (dorsal anterior insula and frontal operculum/precentral gyrus) T' 1-2 (ventral insula)	R′ 6–8 (precentral gyrus) T′ 1–2 (ventral insula)	R′ 1–9 T′ 1–3 = SOZ	SF (40-month follow-up)
3		X' 1-2 (Posterior cingulate)	No fast activity at seizure onset	X′ 1–2 = SOZ	NSF (recurrence in 1 month)

TABLE 3 (Continued)

Subject	Implantation map	SOZ electrode contacts	A posteriori-identified PEZ electrode contacts	Laser-ablated electrode contacts	SF/NSF
4		L' 1-6 (mesial frontal cortex/ superiror frontal gyrus) G' 1-3 (anterior cingulate) M' 5-8 (precentral gyrus/ superior frontal gyrus)	L′ 5–7 (superior frontal gyrus) G′ 1–4 (anterior cingulate) G′ 6–10 (lateral middle frontal gyrus) M′ 6–9 (precentral gyrus/superior frontal gyrus)	L′ 3–4 (mesial frontal cortex) G′ 1–2 (anterior cingulate)	NSF (recurrence in 16 months)
5		M 1–14 (supplementary motor cortex, precentral gyrus/ superior frontal gyrus) P 1–4 (precuneus) R 4–7 (frontal operculum/ precentral gyrus) S 1–2 (posterior dorsal insula)	M 3–4 (supplementary motor cortex) M 6–7, M 10–11 (precentral gyrus/ superior frontal gyrus) P 2–5 (precuneus) R 4–5, 8–9 (frontal operculum/ precentral gyrus) Z 7–8 (intraparietal sulcus)	R 1–8 (dorsal anterior insula/frontal operculum/precentral gyrus) S 1–8 (posterior dorsal insula/parietal operculum)	NSF (recurrence in 9 months)
6		X′ 1–2 (ventral anterior insula) Q′ 1–4 (dorsal anterior insula) Y′ 1–2 (mesial frontal cortex) Z′ 1–2 (mesial frontal cortex)	Y′ 1–9 (mesial frontal cortex/superior frontal sulcus) Z′ 1–3 (mesial frontal cortex)	X′ 1–2 (ventral anterior insula) Y′ 1–3 (mesial frontal cortex)	NSF (recurrence in 1 month)

(Continues)

TABLE 3 (Continued)

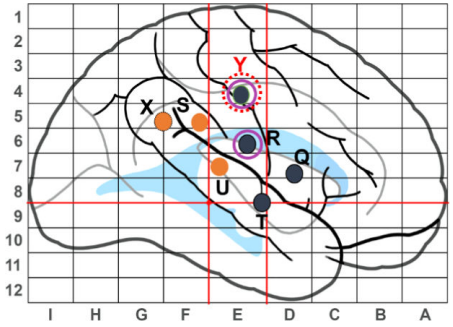
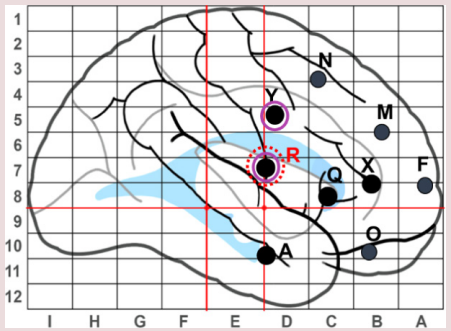
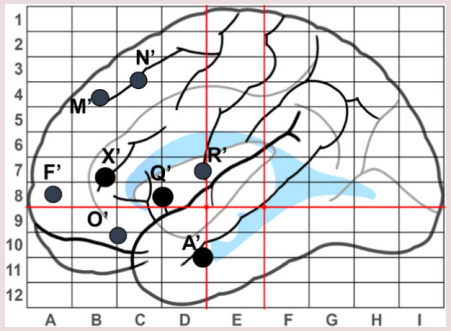
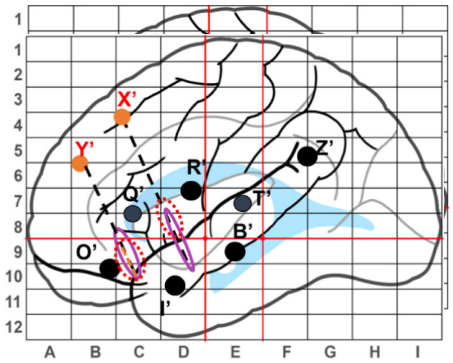
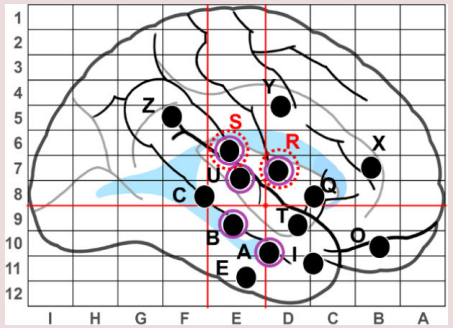
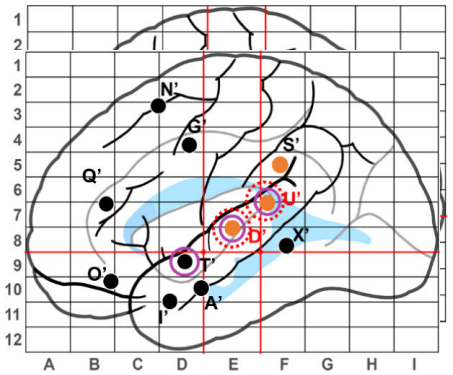
Subject	Implantation map	SOZ electrode contacts	A posteriori-identified PEZ electrode contacts	Laser-ablated electrode contacts	SF/NSF
7		R 1–8 (posterior insula/ parietal operculum/ precentral gyrus) Y 2–3 (midcingulate) Y 10–14 (postcentral gyrus)	S 3–4 (posterior insula) S 13–14 (parietal operculum) U 4–5 (ventral posterior insula) X 8–9 (supramarginal gyrus)	Y 13–14 (postcentral gyrus)	NSF (recurrence in 1 month)
8	 	R 1–4 (anterior dorsal insula) Y 2–5 (anterior cingulate)	No fast activity at seizure onset	R 1–3 (anterior dorsal insula)	NSF (recurrence in 2 months)

TABLE 3 (Continued)

Subject	Implantation map	SOZ electrode contacts	A posteriori-identified PEZ electrode contacts	Laser-ablated electrode contacts	SF/NSF
9		Y′ 1–4 (posterior orbitofrontal) X′ 1–4 (anterior insula)	Y′ 1–3 (posterior orbitofrontal) X′ 5–6 (anterior insula)	Y′ 1–3 (posterior orbitofrontal) X′ 3–4 (anterior insula)	NSF (recurrence in 42 months)
10		R 1–4 (dorsal anterior insula) S 1–4 (dorsal posterior insula) U 1–4 (ventral posterior insula) A 1–4 (amygdala) B 1–4 (hippocampus)	No prediction	R 1–9 (dorsal anterior insula/frontal operculum) S 1–2 (dorsal posterior insula)	NSF (seizure recurrence in 1 month followed by 40 months of seizure freedom)
11		D 1–4 (right posterior insula) T 1–4 (right anterior insula) U 1–4 (right posterior insula) D′ 1–4 (left posterior insula) T′ 1–4 (left anterior insula) U′ 1–4 (left posterior insula)	D 1–2 (right posterior insula) T 2–3 (right anterior insula) D′ 1–3 (left posterior insula) S′ 10–11 (left parietal operculum) U′ 3–5 (left posterior insula)	D′ 1–2 (left posterior insula) U′ 1–2 (left posterior insula)	NSF (recurrence in 44 months)

(Continues)

TABLE 3 (Continued)

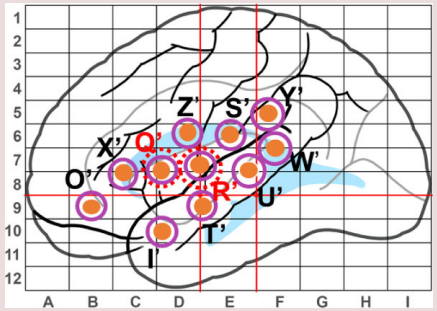
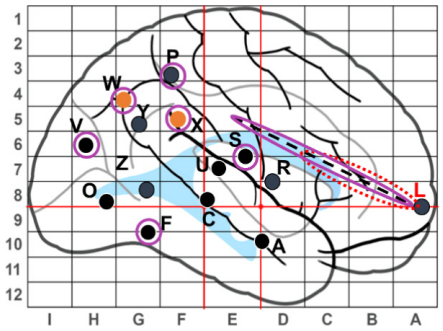
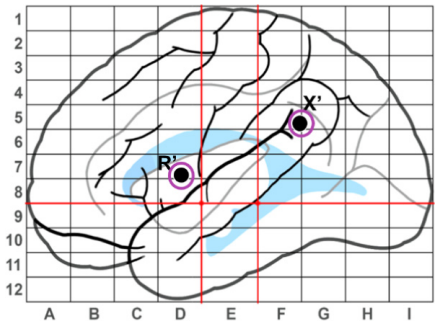
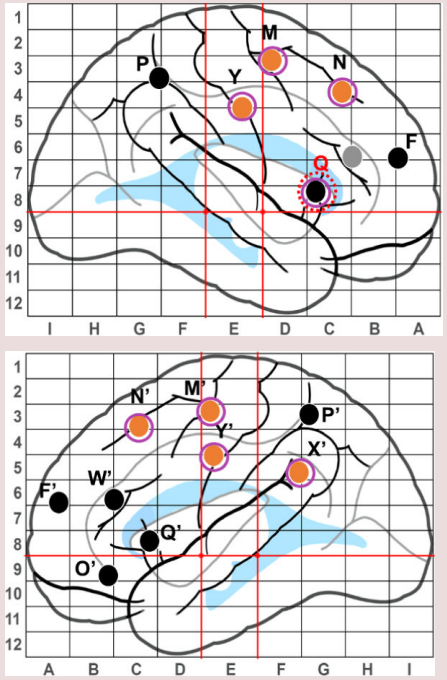
Subject	Implantation map	SOZ electrode contacts	A posteriori-identified PEZ electrode contacts	Laser-ablated electrode contacts	SF/NSF
12		All contacts	I′ 4–5 O′ 8–11 Q′ 2–8 R′ 2–10 S′ 1–5, 8–10 T′ 3–5 U′ 2–7 U′ 9–10 W′ 2–8 X′ 2–4 Y′ 3–9 Z′ 3–7	Q′ 1–8 (anterior dorsal insula and frontal operculum) R′ 2–9 (posterior insula and parietal operculum) Both Q′ and R′ were in polymicrogyria	NSF (recurrence in 7 months)
13	 	X′ 1–2 R′ 3–8 L 1–10 P 9–15 W 7–14 X 5–10 S 1–10 V 6–10 F 5–10	W9–W14 (intraparietal sulcus) X8–X10 (supramarginal sulcus)	L 6–10 (periventricular heterotopia)	NSF (recurrence in 40 months)

TABLE 3 (Continued)

Subject	Implantation map	SOZ electrode contacts	A posteriori-identified PEZ electrode contacts	Laser-ablated electrode contacts	SF/NSF
14		Y 1–16 Y′ 1–16 N 1–10 N′ 1–10 M 1–10 M′ 1–10 Q 1–8 X′ 1–3	M 1–5, M7–M8 M′ 1–10 N 1–5 N′ 1–3, N′ 6–7 X′ 1–8 Y 2–10 Y 3–14 Y′ 2–5, Y′ 7–13, Y′ 15–16	Q 1–8 (anterior insula and frontal operculum)	NSF (recurrence in 1 month)

(Continues)

TABLE 3 (Continued)

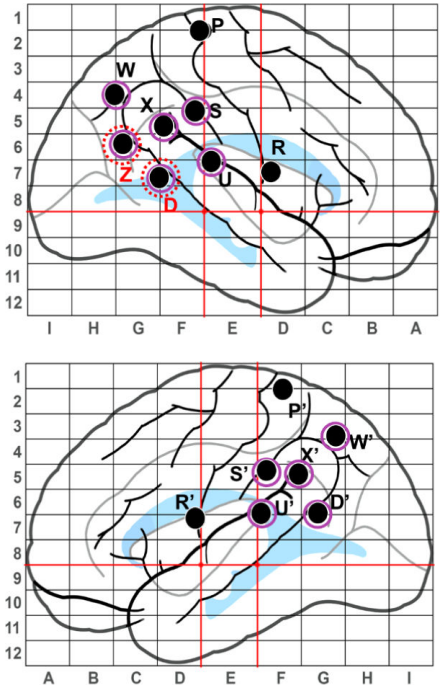
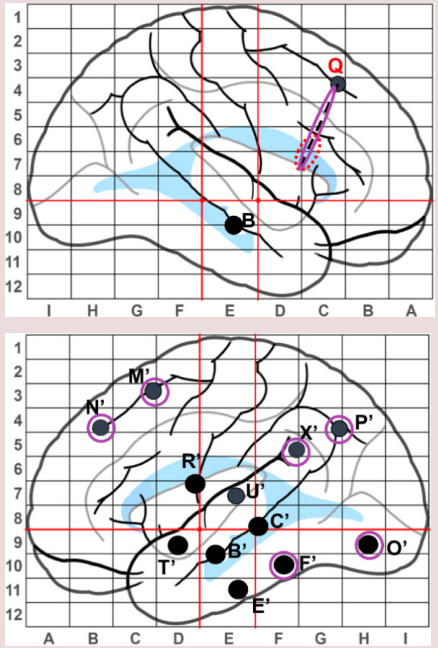
Subject	Implantation map	SOZ electrode contacts	A posteriori-identified PEZ electrode contacts	Laser-ablated electrode contacts	SF/NSF
15		D 1–10 D′ 1–15 S 1–5, 10–15 S′ 1–5, 7–15 U 1–8 U′ 1–8 W 1–12 W′ 1–12 X 11–13 X′ 11–13 Z 10–15	No prediction	D 4–10 (superior temporal sulcus/angular gyrus) Z 5–13 (superior temporal sulcus/angular gyrus)	NSF (recurrence in 1 month)

TABLE 3 (Continued)

Subject	Implantation map	SOZ electrode contacts	A posteriori-identified PEZ electrode contacts	Laser-ablated electrode contacts	SF/NSF
16		Q 1–8 N′ 1–8 M′ 1–8 P′ 1–8 X′ 1–4 F′ 1–10 O′ 3–10	No fast activity at seizure onset	Q 1–2 (questionable periventricular white matter lesion)	NSF (recurrence in 1 month)

Abbreviations: NSF, non-SF; PEZ, predicted epileptogenic zone (a posteriori-identified epileptogenic zone electrode contacts using the "EZ fingerprint" pipeline); SF, seizure-free; SOZ: seizure onset zone.

3.2.3 | Correlation between duration of seizure freedom and proportion of ablated PEZ

In 11 patients with identified PEZ, a correlation analysis was conducted between the duration of seizure freedom and the percentage of ablated PEZ contacts (Figure 3). Patients with close overlap between PEZ and SOZ and significant ablation of PEZ contacts (Subjects 1, 2, 4, 9, 11) showed longer seizure-free periods. In contrast, patients with distant or partial overlap of PEZ and SOZ (Subjects 5, 6) had only brief seizure freedom. One patient with nonlocalized PEZ (Subject 12) experienced early seizure recurrence due to incomplete ablation. Among patients with ablation outside the PEZ, two had early recurrence, whereas one achieved 40 months of seizure freedom after PVH ablation. These findings emphasize the importance of accurately targeting and fully ablating PEZ contacts for improved seizure outcomes.

4 | DISCUSSION

The current retrospective study describes the long-term outcome of SEEG-guided LITT in neocortical DRE. Our results indicate that the optimal candidates for SEEG-guided LITT in neocortical DRE are patients with a limited, well-localized PEZ that is colocalized with the SOZ identified by conventional analysis. Our study emphasizes that the complete ablation of the PEZ is crucial for a favorable outcome. We also observed that in patients whose PEZ was not identified or was discordant with the SOZ or laser-ablated contacts, LITT was not effective. The majority of these patients had seizure recurrence within 1 or 2 months.

Studies showed that LITT in patients with MRI-negative epilepsies had poor seizure outcomes,[12–16] and SEEG could be applied to improve the precision of the localization of the EZ and the targets for LITT. Only a few published studies have addressed the role of electrophysiologic biomarkers of the EZ to guide LITT, especially in nonlesional epilepsy. A recent paper investigated the value of FA at seizure onset in lesional or nonlesional mesial temporal lobe epilepsy.[25] The study showed that having sustained FA only in the ablated mesial temporal electrodes correlated with favorable seizure outcomes (Engel 1A and 1B).[25] In contrast, sustained FA in extramesial temporal nonablated intracranial electrodes was associated with poor outcome.[25] Gupta et al.[11] studied 24 lesional and nonlesional neocortical epilepsy patients who underwent LITT, examining the correlation between low-voltage FA (LVFA) electrophysiologic seizure onset pattern and seizure outcome at a 1-year follow-up after ablation. Six of 10 patients with LVFA achieved favorable seizure outcomes (Engel 1). Out of the remaining 11 patients with different frequency patterns, such as evolving rhythmic spikes or rhythmic alpha, theta, and delta frequencies, only one patient achieved an Engel 1 outcome.[11] This observation aligned with our study finding in which six of 13 patients with LVFA had Engel 1 outcome at 1-year follow-up.

Within our cohort, which primarily consisted of patients (13/16) exhibiting LVFA at seizure onset, we

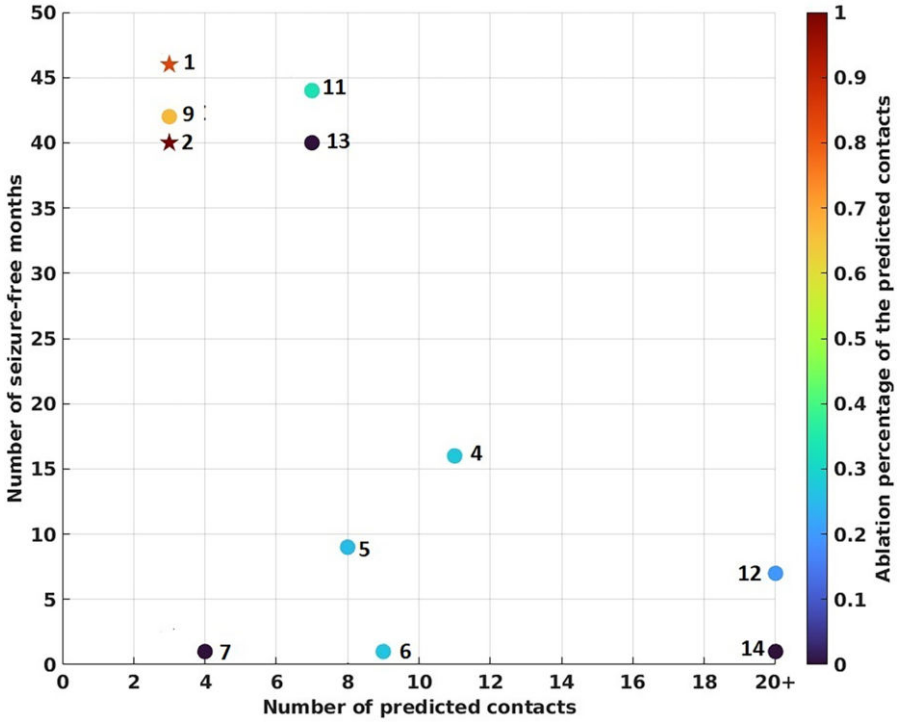


FIGURE 3 Correlation of the number of detected predicted epileptogenic zone (PEZ) contacts (bipolar pair), the duration of seizure freedom (months), and the proportion of the ablated PEZ contacts (color-coded map with red representing complete ablation of PEZ and black representing ablation of outside PEZ or no PEZ identified) in 11 patients with a posteriori-identified PEZ. Patients without seizure recurrence are marked with stars.

observed that identifying a limited and well-localized PEZ was the strongest predictor for favorable seizure outcomes. We observed that the percentage of ablated PEZ contacts demonstrated a strong correlation with the duration of seizure freedom (Figure 3). The majority of the patients with LVFA for whom the PEZ was not identified, or ablation was performed outside the PEZ, had early seizure recurrence, except for the patient with PVH (Table 2). Similar to this patient, one patient without PEZ identified had a beneficial outcome, with long-term seizure freedom on medications despite early recurrence. Here, our results highlight the value of the "EZ fingerprint" analysis of SEEG data in further identifying the better target for LITT in patients with LVFA but also reveal some limitations of using the "EZ fingerprint" pipeline in routine clinical practice.

LITT is preferred in patients with deep-seated localized and restricted EZ, such as in insular–opercular scenarios, as it carries a potentially lower risk of complication compared to open resective surgery due to postresection ischemic infarcts caused by disruption of the blood supply to the corona radiata, especially in the dorsal and posterior insulo-opercular regions.[11,26] In previously published data, seizure freedom was achieved in 53%–69% of patients who underwent either resection[27] or laser/radiofrequency ablation of the insulo-opercular regions.[11,26,28] Most of the previously published cohorts had associated lesions in the insulo-opercular region. However, there are limited data on the seizure outcome solely on nonlesional insulo-opercular epilepsy. Gupta et al.[11] reported poor outcomes in patients with EZ localized in the insular region, which was not observed in our study. In our cohort, we did not find a correlation of seizure outcome with the anatomical location of the EZ. Of 16 patients, nine patients (one lesional [polymicrogyria] and eight nonlesional extratemporal lobe epilepsy) underwent LITT in the insulo-opercular region (Table 3). Of nine patients, three had a well-localized PEZ and SOZ and achieved an average of 42 months of seizure freedom, with one patient having no seizure recurrence at the last follow-up. In six patients for whom the PEZ was not identified or was distantly or diffusely located, or LITT was performed outside the PEZ, seizures recurred within an average of 2 months (range = 1–7). Accordingly, our study suggests that LITT can be a reasonable therapeutic option in patients with well-localized EZ in neocortical regions with surgical/anatomic constraints for open resection, such as the insulo-opercular areas.

Although the "EZ fingerprint" pipeline further complements the available LITT literature in better determining candidacy for LITT, we released neither this pipeline nor the trained prediction model for any commercial usage or clinical diagnostic purpose. Moreover, the data collection, processing, and analysis must be conducted carefully on a case-by-case basis by well-trained staff. However, to facilitate epilepsy investigational studies, we had publicly released, for research only, EZ Fingerprint software with a graphic user interface and a corresponding series of tutorials so that clinicians and researchers who do not have sufficient coding skills would be able to process and analyze their own data easily.[24] With all the limitations, analysis of the SEEG data with the "EZ fingerprint" pipeline can better determine the candidacy for LITT, that is, as a patient selection tool, guiding and optimizing the necessary target for LITT.[21,22,24]

5 | LIMITATIONS

Limitations of our study include the small size of the cohort and its retrospective nature, which call for caution in the interpretation of the results. Larger prospective studies are necessary to validate these findings. A similarly important limitation is the intrinsic constraints associated with using the "EZ fingerprint" pipeline. The SVM classifier used in the pipeline was developed based on a limited original set of only 17 patients with gamma activity at seizure onset, with specific frequency ranges (maximum frequency range of 97 Hz and a median of the minimum frequency range of 43 Hz).[21,22] Consequently, variations in FA patterns that were not observed in the original set may lead to false negative predictions, as observed in patients where no PEZ contact was identified.

Invasive monitoring methods, such as SEEG, suffer from inherent limitations in spatial resolution, which may result in the SOZ and PEZ originating from cortical areas not covered by the electrodes. This limitation hampers precise estimation of the EZ volume and makes it challenging for physicians to determine the optimal ablation volume required for a patient's cure.

To overcome these limitations, further research is needed to enhance our understanding of EZ biomarkers and to refine postprocessing analysis techniques, such as the "EZ fingerprint" pipeline, for improved clinical application.

AUTHOR CONTRIBUTIONS

Conception and design: Thandar Aung, Olesya Grinenko, and Jorge Gonzalez-Martinez. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: Thandar Aung and Olesya Grinenko. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Thandar Aung. Statistical analysis: Thandar Aung, Olesya Grinenko, Jian Li, and John C. Mosher. Administrative/technical/

material support: Thandar Aung, Olesya Grinenko. Study supervision: Patrick Chauvel, Jorge Gonzalez-Martinez.

ACKNOWLEDGMENTS

The authors are grateful to all the staff at the Cleveland Clinic for providing the best care to those patients. Especially, the authors would like to thank the following treating physicians whose patients were included in the study: Drs. Juan Bulacio, Imad Najm, Andreas Alexopoulos, Dileep Nair, Lara Jehi, Andrey Stojic, Zhong Ying, Parkash Kotagal, and Ahsan Moosa Naduvil Valappil. The views expressed in this article do not necessarily reflect the opinions of the individuals acknowledged. We are also thankful to the patients and their families for participating in this study.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest regarding the production of this article. J.G.-M. is a consultant for Zimmer-Biomet. The other authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

ORCID

Thandar Aung https://orcid.org/0000-0002-6770-9642

REFERENCES

1. Bown SG. Phototherapy of tumors. World J Surg. 1983;7(6):700–9. https://doi.org/10.1007/BF01655209
2. Rennert RC, Khan U, Tatter SB, Field M, Toyota B, Fecci PE, et al. Patterns of clinical use of stereotactic laser ablation: analysis of a multicenter prospective registry. World Neurosurg. 2018;116:e566–70. https://doi.org/10.1016/j.wneu.2018.05.039
3. Brotis AG, Giannis T, Paschalis T, Kapsalaki E, Dardiotis E, Fountas KN. A meta-analysis on potential modifiers of LITT efficacy for mesial temporal lobe epilepsy: seizure-freedom seems to fade with time. Clin Neurol Neurosurg. 2021;205:106644. https://doi.org/10.1016/j.clineuro.2021.106644
4. Sperling MR, Gross RE, Alvarez GE, McKhann GM, Salanova V, Gilmore J. Stereotactic laser ablation for mesial temporal lobe epilepsy: a prospective, multicenter, single-arm study. Epilepsia. 2020;61(6):1183–9. https://doi.org/10.1111/epi.16529
5. Kang JY, Sperling MR. Magnetic resonance imaging-guided laser interstitial thermal therapy for treatment of drug-resistant epilepsy. Neurotherapeutics. 2017;14(1):176–81. https://doi.org/10.1007/s13311-016-0498-3
6. Hale AT, Sen S, Haider AS, Perkins FF, Clarke DF, Lee MR, et al. Open resection versus laser interstitial thermal therapy for the treatment of pediatric insular epilepsy. Clin Neurosurg. 2019;85(4):E730–6. https://doi.org/10.1093/neuros/nyz094
7. Landazuri P, Shih J, Leuthardt E, Ben-Haim S, Neimat J, Tovar-Spinoza Z, et al. A prospective multicenter study of laser ablation for drug resistant epilepsy – one year outcomes. Epilepsy Res. 2020;167:106473. https://doi.org/10.1016/j.eplepsyres.2020.106473
8. Ross L, Naduvil AM, Bulacio JC, Najm IM, Gonzalez-Martinez JA. Stereoelectroencephalography-guided laser ablations in patients with neocortical pharmacoresistant focal epilepsy: concept and operative technique. Oper Neurosurg. 2018;15(6):656–63. https://doi.org/10.1093/ons/opy022
9. Malcolm J, Stern M, Fasano R, Gross R, Willie J. Stereotactic electroencephalography guided laser ablation for neocortical epilepsy. Stereotact Funct Neurosurg. 2017;95:102.
10. Gupta K, Dickey AS, Hu R, Faught E, Willie JT. Robot assisted MRI-guided LITT of the anterior, lateral, and medial temporal lobe for temporal lobe epilepsy. Front Neurol. 2020;11:572334. https://doi.org/10.3389/fneur.2020.572334
11. Gupta K, Cabaniss B, Kheder A, Gedela S, Koch P, Hewitt KC, et al. Stereotactic MRI-guided laser interstitial thermal therapy for extratemporal lobe epilepsy. Epilepsia. 2020;61(8):1723–34. https://doi.org/10.1111/epi.16614
12. Gonzalez-Martinez JA, Chauvel PY. The importance of orthogonal implantation in SEEG: historical considerations. J Neurosurg. 2021;135:332–3. https://doi.org/10.3171/2020.10.JNS203393
13. Gonzalez-Martinez JA, Chauvel P. The stereoelectroencephalography methodology applied to epilepsies with a visible lesion. Neurosurg Clin N Am. 2020;31(3):387–94. https://doi.org/10.1016/j.nec.2020.03.010
14. Chauvel P. The epileptogenic zone: a critical reconstruction. In: Schuele S, A practical approach to stereo EEG. New York City: Springer Publishing Company; 2020. p. 105–18. https://doi.org/10.1891/9780826136930.0010
15. Chauvel P, Gonzalez-Martinez J, Bulacio J. Presurgical intracranial investigations in epilepsy surgery. In: Handbook of clinical neurology. Amsterdam, The Netherlands: Elsevier; Vol. 161; 2019. p. 45–71. https://doi.org/10.1016/B978-0-444-64142-7.00040-0
16. Duncan JS, Winston GP, Koepp MJ, Ourselin S. Brain imaging in the assessment for epilepsy surgery. Lancet Neurol. 2016;15(4):420–33. https://doi.org/10.1016/S1474-4422(15)00383-X
17. Brown MG, Drees C, Nagae LM, Thompson JA, Ojemann S, Abosch A. Curative and palliative MRI-guided laser ablation for drug-resistant epilepsy. J Neurol Neurosurg Psychiatry. 2018;89(4):425–33. https://doi.org/10.1136/jnnp-2017-316003
18. Wu C, Jermakowicz WJ, Chakravorti S, Cajigas I, Sharan AD, Jagid JR, et al. Effects of surgical targeting in laser interstitial thermal therapy for mesial temporal lobe epilepsy: a multicenter study of 234 patients. Epilepsia. 2019;60(6):1171–83. https://doi.org/10.1111/epi.15565
19. Kerezoudis P, Parisi V, Marsh WR, Kaufman TJ, Lehman VT, Worrell GA, et al. Surgical outcomes of laser interstitial thermal therapy for temporal lobe epilepsy: systematic review and meta-analysis. World Neurosurg. 2020;143:527–536.e3. https://doi.org/10.1016/j.wneu.2020.07.194
20. Grewal SS, Zimmerman RS, Worrell G, Brinkmann BH, Tatum WO, Crepeau AZ, et al. Laser ablation for mesial temporal epilepsy: a multi-site, single institutional series. J Neurosurg. 2019;1306(6):2055–62. https://doi.org/10.3171/2018.2.JNS171873
21. Grinenko O, Li J, Mosher JC, Wang IZ, Bulacio JC, Gonzalez-Martinez J, et al. A fingerprint of the epileptogenic zone in human epilepsies. Brain. 2018;141(1):117–31. https://doi.org/10.1093/brain/awx306

22. Li J, Grinenko O, Mosher JC, Gonzalez-Martinez J, Leahy RM, Chauvel P. Learning to define an electrical biomarker of the epileptogenic zone. Hum Brain Mapp. 2020;41(2):429–41. https://doi.org/10.1002/hbm.24813
23. Laitinen L. Co-planar stereotaxic atlas of the human. Brain. 1989;91:277–8. https://doi.org/10.1016/0303-8467(89)90128-5
24. Jian Li. Epileptogenic Zone Fingerprint. Available from: https://silencer1127.github.io/software/EZ_Fingerprint/ezf_main (2018). Accessed Jan 2018.
25. Zaher N, Urban A, Antony A, Plummer C, Bagić A, Richardson RM, et al. Ictal onset signatures predict favorable outcomes of laser thermal ablation for mesial temporal lobe epilepsy. Front Neurol. 2020;11:595454. https://doi.org/10.3389/fneur.2020.595454
26. Gireesh ED, Lee K, Skinner H, Seo J, Chen PC, Westerveld M, et al. Intracranial EEG and laser interstitial thermal therapy in MRI-negative insular and/or cingulate epilepsy: case series. J Neurosurg. 2021;135(3):751–9. https://doi.org/10.3171/2020.7.JNS201912
27. Weil AG, Le NMD, Jayakar P, Resnick T, Miller I, Fallah A, et al. Medically resistant pediatric insular-opercular/perisylvian epilepsy. Part 2: outcome following resective surgery. J Neurosurg Pediatr. 2016;18(5):523–35. https://doi.org/10.3171/2016.4.PEDS15618
28. Mullatti N, Landre E, Mellerio C, Oliveira AJ, Laurent A, Turak B, et al. Stereotactic thermocoagulation for insular epilepsy: lessons from successes and failures. Epilepsia. 2019;60(8):1565–79. https://doi.org/10.1111/epi.16092

How to cite this article: Aung T, Grinenko O, Li J, Mosher JC, Chauvel P, Gonzalez-Martinez J. Stereoelectroencephalography-guided laser ablation in neocortical epilepsy: Electrophysiological correlations and outcome. Epilepsia. 2023;00:1–19. https://doi.org/10.1111/epi.17739