Robot-assisted stereoelectroencephalography in children

Robert A. McGovern, MD, Elia Pestana Knight, MD, Ajay Gupta, MD, Ahsan N. V. Moosa, MD, Elaine Wyllie, MD, William E. Bingaman, MD, and Jorge Gonzalez-Martinez, MD, PhD

Epilepsy Center, Cleveland Clinic Foundation, Cleveland, Ohio

OBJECTIVE The goal in the study was to describe the clinical outcomes associated with robot-assisted stereoelectroencephalography (SEEG) in children.

METHODS The authors performed a retrospective, single-center study in consecutive children with medically refractory epilepsy who were undergoing robot-assisted SEEG. Kaplan-Meier survival analysis was used to calculate the probability of seizure freedom. Both univariate and multivariate methods were used to analyze the preoperative and operative factors associated with seizure freedom.

RESULTS Fifty-seven children underwent a total of 64 robot-assisted procedures. The patients' mean age was 12 years, an average of 6.4 antiepileptic drugs (AEDs) per patient had failed prior to implantation, and in 56% of the patients the disease was considered nonlesional. On average, children had 12.4 electrodes placed per implantation, with an implantation time of 9.6 minutes per electrode and a 10-day postoperative stay. SEEG analysis yielded a definable epileptogenic zone in 51 (89%) patients; 42 (74%) patients underwent surgery, half of whom were seizure free at last follow-up, 19.6 months from resection. In a multivariate generalized linear model, resective surgery, older age, and shorter SEEG-related hospital length of stay were associated with seizure freedom. In a Cox proportional hazards model including only the children who underwent resective surgery, older age was the only significant factor associated with seizure freedom. Complications related to bleeding were the major contributors to morbidity. One patient (1.5%) had a symptomatic hemorrhage resulting in a permanent neurological deficit.

CONCLUSIONS The authors report one of the largest pediatric-specific SEEG series demonstrating that the modern surgical management of medically refractory epilepsy in children can lead to seizure freedom in many patients, while also highlighting the challenges posed by this difficult patient population.

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KEYWORDS stereoelectroencephalography; pediatric epilepsy; robotic surgical procedures; electrodes; brain mapping

CHILDREN with epilepsy typically experience good control of their disease with antiepileptic drugs (AEDs), because AEDs are efficacious in approximately 75% of children with new-onset epilepsy.⁹ However, in 20% of children with focal epilepsy the disease will become medically refractory or pharmacoresistant.²⁴ In children with early brain lesions and poorly localized or generalized epileptiform abnormalities, a potentially epileptogenic lesion on MRI may be the primary determinant for surgical candidacy provided the presurgical data evaluation is concordant. Children in whom a lesion is not demonstrated on MRI or who have discordant clinical or electroencephalography (EEG) data will probably

then undergo a more detailed noninvasive evaluation that includes some combination of magnetoencephalography (MEG), FDG-PET, ictal SPECT, genetic/metabolic testing, and neuropsychological testing—depending on the child's age, developmental milestones, and ability to cooperate with testing.

If the noninvasive evaluation indicates a focal epilepsy and has generated plausible hypotheses as to the possible anatomical locations of the involved epileptogenic networks, the child is a good candidate for invasive monitoring with a technique such as stereoelectroencephalography (SEEG). The SEEG technique has become much more commonly used in North American centers over the last decade, par-

ABBREVIATIONS AED = antiepileptic drug; EZ = epileptogenic zone; LOS = length of hospital stay; MEG = magnetoencephalography; PMC = patient management conference; SEEG = stereoelectroencephalography.

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ticularly with the use of robotic assistance, because this technical adjunct has resulted in a faster and more efficient method of placing electrodes.¹⁴ Unfortunately, almost all of the current literature on its safety and efficacy either has focused exclusively on adults or includes only a few children as part of a larger cohort.^{8,14} As a result, there is a paucity of literature describing SEEG specifically in pediatric patients with epilepsy.^{10,17,20} A recent systematic review detailing every English-language SEEG study published through the first quarter of 2015 included 4000 patients, of whom approximately 300 were children.⁷ In addition, there are currently no papers that specifically describe the clinical outcomes of robot-assisted SEEG in pediatric patients. Since our initial study detailing the frame-based SEEG experience in pediatric and adolescent patients at our center,¹⁵ we have refined the technical aspects of surgery, including using robotic assistance as our primary method of electrode placement. We have also expanded the indications for performing SEEG in children as we have accumulated surgical experience and better understood its capabilities and limitations. Here we detail our SEEG experience in children in whom robotic assistance was used.

Methods

We studied consecutive pediatric patients (< 18 years old) who had medically refractory epilepsy and who underwent SEEG implantation performed using robotic assistance at the Cleveland Clinic's Epilepsy Center between June 2011 and July 2017. All procedures were performed as part of standard clinical care. This study was approved by the Cleveland Clinic Institutional Review Board.

Study Variables

Demographic, preoperative, operative, and postoperative data were collected prospectively and analyzed retrospectively. High-resolution, epilepsy protocol, brain MRIs (volumetric T1-weighted coronal and axial FLAIR studies) were performed for all patients on either 1.5-T or 3-T systems (Siemens). All imaging studies were reviewed by a board-certified neuroradiologist, and the decision whether to consider the MRI findings as lesional was determined by the reading of the neuroradiologist and the consensus of the entire study group during the patient's epilepsy case management conference. Postoperative clinical data were obtained by patient interview during regularly scheduled clinic visits or by telephone. Seizure outcome data were obtained through our internal, independent Epilepsy Center Outcomes Registry (ECOR), which calculated monthly pre- and postoperative seizure frequency and verified all of the seizure outcomes, including time to recurrence with most recent follow-up dates. Postoperative CT scans were reviewed for every patient after both placement and removal of electrodes in order to determine hemorrhagic complications. The clinical chart including inpatient daily progress notes and postoperative office visits documenting neurological examination findings was reviewed to determine postoperative complications.

Selection Criteria and Implantation Technique

The selection criteria, exploration strategies, and im-

plantation technique performed using robotic assistance have been discussed in detail in prior publications by our group and others.^{5,8,15} In brief, the recommendations for SEEG implantation were made during our multidisciplinary patient management conference (PMC) after review and discussion of the patient's noninvasive evaluation. Typically, the selection criteria for SEEG implantation include a testable hypothesis that indicates a focal epilepsy, the possibility of a deep-seated epileptogenic zone (EZ), the need for bihemispheric evaluation, and/or a noninvasive evaluation indicative of functional network involvement (e.g., limbic system) in the setting of an MRI study that does not demonstrate a lesion.² A T1-weighted volumetric MRI sequence with gadolinium (slice thickness 1 mm, voxel size 0.41 mm × 0.41 mm × 1 mm) and a CTA study are obtained before surgery. We still consider the CTA necessary both for avascular planning and for facial registration purposes because the facial reconstruction based on MRI is occasionally suboptimal. All of the trajectory planning is performed in the robotic software suite (ROSA; MedTech/Zimmer Biomet) the day prior to surgery. Trajectories are planned based on the preimplantation hypotheses of the EZs. These are generated during the preimplantation PMC and take into account the potential anatomical locations of ictal onset zones and regions of early seizure spread.

On the day of surgery, under general anesthesia, the patient is placed in the supine position and the head is placed in a neutral position. A Leksell frame (Elekta) is attached to the head, but is used solely for fixation purposes as the patient is then fixed into place on the operating room table. The patient's face is then registered using semiautomatic laser-based facial recognition to register the preoperative volumetric MRI or CTA study. Once a satisfactory registration with the robot has been confirmed, the patient is prepared and draped in the usual sterile fashion. The robot is then used to create twist drill holes, with guide bolts screwed firmly into place for every trajectory. Once all of the bolts are in place, the electrodes are placed using a stylet (0.8 mm), followed by insertion of the premeasured electrode (PMT Corp.) for each trajectory. A portable skull radiograph is obtained at the end of the operation to ensure that all of the electrodes are in the proper locations. Next, all of the electrodes are connected to a mobile electrocorticography recording setup and examined to ensure that each electrode is recording cortical activity.

The patient undergoes a postoperative CT scan in the postanesthesia care unit. After recovery in the postanesthesia care unit, the patient is brought to the epilepsy monitoring unit for clinical and intracranial EEG monitoring. The patient is placed on his or her home AEDs and then weaned off until a sufficient number of typical seizures occur. A second PMC is held to discuss whether the EZ can be localized and whether a resective strategy can be formulated. The patient is then taken back to the operating room for electrode removal and a postremoval CT scan is performed. He or she is discharged home the day after electrode removal and returns 6 weeks later to undergo a craniotomy for tailored resection of the potential EZ, as determined by the second PMC. After recovery from resective surgery, the patient is discharged home and returns for 6-week, 6-month, and yearly follow-up visits.

Data Analysis

A database maintaining all of the relevant variables was kept in Microsoft Excel and transferred to JMP 13 (SAS Institute) for statistical analysis. More specifically, the distribution of demographic statistics was calculated. Univariate analysis was initially performed in the overall group by using unpaired t-tests for normally distributed variables and Wilcoxon rank-sum, chi-square, and Fisher exact tests for nonnormally distributed variables to find predictors of seizure outcome. Variables with a p value of < 0.10 on initial univariate analysis were then tested in a multivariate nominal logistic model. When analyzing this model, the “resective surgery” variable quasi-completely separated the seizure outcome data. To rectify this, we used a generalized linear model with a Firth penalized maximum likelihood estimation. This method allows for unbiased parameter estimates and appropriately calculated p values. Results were then reported as parameter estimates, chi-square likelihood ratios, and p values. Kaplan-Meier survival analysis was used to calculate the probability of seizure freedom in the patients who underwent resective surgery. A Cox proportional hazards model was then calculated using the significant risk factors on univariate analysis. A p value of < 0.01 was considered significant in both parameter estimate and proportional hazards calculations. The GNU Image Manipulation Program (GIMP, version 2.8.18) was used to help create the figures.

Results

Patient Demographics

Fifty-seven children underwent a total of 64 robot-assisted SEEG procedures. The mean age was 12 years and patients with Engel I outcomes were significantly older (13.5 vs 11.2 years, Engel I vs Engel $> I$; $p = 0.02$, unpaired t-test, Table 1). On average, 6.4 AEDs per patient had failed prior to implantation, with a mean duration of epilepsy of 77 months (range 10–207 months). According to MRI findings, seizures were considered nonlesional in 32 children (56%). Eighteen patients (32%) had undergone epilepsy surgery of some type prior to SEEG evaluation, most commonly subdural grids/strips with or without a subsequent resection.

Operative Variables

In total, 791 electrodes were implanted for an average of 12.4 electrodes per implantation (Table 2). Twenty-seven implantations were solely left hemispheric, 11 were right hemispheric, and 26 were bihemispheric. Operating time was 117 (± 35) minutes per implantation, meaning that the time per electrode was 9.6 (± 2.4) minutes. The mean estimated blood loss was 5.3 (± 5) ml. The mean length of hospital stay (LOS) for the monitoring period was 10 days, with the Engel I group staying for a significantly shorter period of time (8.1 vs 11 days, Engel I vs Engel $> I$; $p = 0.04$, unpaired t-test, Table 2). SEEG analysis of interictal findings and seizures was able to define the EZ with a concordant anatomical-electrical-functional correlation in 54 patients (95%, Fig. 1). Of the 3 children whose EZ could not be defined, 2 had no seizures during their stay and

1 had a symptomatic intraparenchymal hemorrhage that required emergency lead removal and hematoma evacuation. Of the 54 patients whose seizures were recorded with a defined EZ, 42 (74% of the entire group) underwent a total of 48 resective surgeries guided by the robot-assisted SEEG evaluation (Fig. 1, Table 3). Of the remaining 12 children, 3 had diffuse hemispheric onset, 4 had bilateral independent ictal onset, and 5 patients deferred surgery because of the risk of a permanent neurological deficit (typically hemianopia or motor deficit).

Clinical Outcome and Pathology

Kaplan-Meier survival analysis demonstrates seizure recurrence for all 42 patients in Fig. 2. Of the 42 children who underwent resection, 50% had Engel class I outcomes (Fig. 1, Table 3) at a mean follow-up of 23.4 months from SEEG and 19.6 months from the most recent resection. In order to follow the natural history of these patients, we categorized them at different time points. At 1 month postresection, all 42 patients were available for follow-up and 76% were seizure free. For the 36 patients available for follow-up at 6 months, 53% were seizure free. At 12 months postoperatively, 21 patients were available for follow-up and 48% were seizure free. At 24 months postoperatively, 13 patients were available for follow-up and 46% were seizure free. By 48 months postoperatively, only 3 patients were available for follow-up and 2 of them were seizure free. Thus, 17 of 21 surgical failures occurred within 6 months after resection.

Resective surgery was associated with significantly improved outcome (100% vs 58%, Engel I vs Engel $> I$; $\chi^2 = 16.8$, $p < 0.0001$; using Fisher's exact test, $p = 0.0003$). Seizure frequency improved from a median of 13.5 seizures per month to 0.6 seizures per month in the overall group. Of note, after the initial surgery, 17 of 42 children were seizure free. Another 4 patients improved to Engel class I after a second resective surgery. The other 2 patients who had a second resection remained Engel class III and IV at last follow-up. Twenty-nine percent of patients were Engel class IV at last follow-up. Of the 15 children who did not undergo resection, none were seizure free. Four were lost to follow-up. Pathological diagnosis revealed focal cortical dysplasia in 81% of cases. No abnormality was found only in children with poor seizure outcomes (Table 3). In a multivariate generalized linear model including all of the patients in the study, resective surgery, older age, and shorter LOS during SEEG were predictive of seizure outcome (Table 4). In the Cox proportional hazards model only including children undergoing resective surgery, older age was the only factor predictive of seizure outcome.

Complications

Complications related to bleeding are the major contributors to the morbidity of SEEG. In this series of 64 implantations including 791 electrodes, we had 1 major intraparenchymal hemorrhage requiring removal of electrodes and hematoma evacuation. This patient was left with permanent hand weakness. There were 5 other bleeding events related to SEEG implantation, including

TABLE 1. Univariate analysis of preoperative clinical, imaging, and scalp EEG findings in the seizure-free and recurrence groups

Variable	Overall, n = 57	Engel I, n = 21	Engel >I, n = 36	p Value
Age at SEEG in yrs, mean ($\pm$ SD)	12 ($\pm$ 3.6)	13.5 ($\pm$ 3.8)	11.2 ($\pm$ 3.3)	0.02
Sex, F/M	32:25	13:8	19:17	0.50
Presumed etiology, no. (%)				0.52
Unknown; normal MRI	32 (56%)	11 (52%)	21 (58%)	
Malformation of cortical development	15 (26%)	6 (29%)	9 (25%)	
Encephalitis	4 (7%)	1 (5%)	3 (8%)	
Other	6 (11%)	3 (14%)	3 (8%)	
Duration of epilepsy in mos, mean ($\pm$ SD)	77.6 ($\pm$ 46)	70.2 ($\pm$ 47)	80.9 ($\pm$ 46)	0.41
Preop seizure frequency, no. (%)				0.60
Daily	32 (56%)	10 (48%)	22 (61%)	
Weekly	23 (40%)	10 (48%)	13 (36%)	
Monthly	2 (4%)	1 (5%)	1 (3%)	
Failed AEDs, mean ($\pm$ SD)	6.4 ($\pm$ 2.5)	5.5 ($\pm$ 2.3)	6.8 ($\pm$ 2.5)	0.06
Interictal scalp EEG, no. (%)				0.71
Ipsilat spikes only	30 (53%)	12 (57%)	18 (50%)	
Bilat spikes	17 (30%)	6 (29%)	11 (31%)	
Contralat spikes only	2 (4%)	1 (5%)	1 (3%)	
No spikes	6 (11%)	2 (10%)	4 (11%)	
Scalp ictal EEG onset, no. (%)				0.35
Ipsilat	33 (58%)	13 (62%)	20 (56%)	
Bilat	10 (18%)	3 (14%)	7 (19%)	
Vertex	7 (12%)	1 (5%)	6 (17%)	
Contralat	2 (4%)	1 (5%)	1 (3%)	
Nonlocalizable	4 (7%)	3 (14%)	1 (3%)	
No change	1 (2%)	0 (0%)	1 (3%)	
Nonlesional MR images, no. (%)	32 (56%)	9 (43%)	23 (64%)	0.13
Supplementary studies, no. (%)				
MEG	40 (70%)	14 (67%)	26 (72%)	0.66
PET	55 (97%)	20 (95%)	35 (97%)	0.70
Ictal SPECT	36 (63%)	10 (48%)	26 (72%)	0.06
All 3 studies; MEG, PET, & SPECT	26 (46%)	8 (38%)	18 (50%)	0.38
Prior epilepsy surgery, no. (%)	19 (33%)	5 (24%)	14 (39%)	0.24

subdural hematoma and intraparenchymal hemorrhage, which were small and asymptomatic. As a result, 9.4% of implantations had some type of bleeding event, with a risk of 0.8% per electrode, and 1.5% of implantations had a symptomatic hematoma with permanent neurological deficit, for a risk of 0.1% per electrode. There were no infections. One child did pull out the electrodes and had to have them removed and replaced at a later date. There were no statistically significant predictors of complications related to SEEG electrode placement. Postoperative deficits related to resections were typical for the region of cortex removed. Seven patients had transient weakness or a supplementary motor area syndrome that improved postoperatively, whereas 3 patients had permanent weakness. In all of these cases, patients and families were counseled as to the likelihood of these anticipated deficits and elected to proceed with surgery in the attempt to achieve seizure freedom.

Discussion

SEEG was developed in the 1950s by Bancaud and colleagues^{5,6} as a methodology for invasively mapping seizure-onset regions in patients with medically refractory epilepsy. Although the underlying principles remain the same, the technical aspects of SEEG are dynamic and have undergone many changes as technology has improved over time.² More specifically, SEEG has become much more commonly used in North American epilepsy centers with the advent of robotic assistance over the last decade and the increasing quality of MRI. These two technical advances have allowed neurosurgeons to use frameless techniques without a formal angiogram to plan and place the depth electrodes. We began using robotic assistance in 2011 after having used a frame-based approach with conventional angiogram and live fluoroscopy as described in Europe.^{10,20,23} This technique immediately resulted in

TABLE 2. Univariate analysis of SEEG operative variables in seizure-free and seizure recurrence groups

Variable	Overall, n = 57	Engel I, n = 21	Engel >I, n = 36	p Value
Mean no. of implantations	1.1 ($\pm$ 0.4)	1 (0)	1.2 ($\pm$ 0.5)	0.06
Mean no. of electrodes placed per patient	13.9 ($\pm$ 4.3)	12.6 ($\pm$ 2.6)	14.6 ($\pm$ 4.9)	0.08
Mean no. of electrodes placed per implantation	12.4 ($\pm$ 2.7)	12.6 ($\pm$ 2.6)	12.9 ($\pm$ 1.8)	0.65
Unilat implantation, no. (%) [*]	41 (64%)	13 (62%)	28 (65%)	0.95
Mean no. of cerebral lobes involved in SEEG hypotheses	2.3 ($\pm$ 0.7)	2.4 ($\pm$ 0.9)	2.3 ($\pm$ 0.6)	0.49
Mean op time, mins [*]	117 ($\pm$ 35)	116 ($\pm$ 31)	123 ($\pm$ 37)	0.44
Mean op time per electrode, mins [*]	9.6 ($\pm$ 2.4)	9.3 ($\pm$ 2.2)	9.6 ($\pm$ 2.5)	0.71
Estimated blood loss, ml [*]	5.3 ($\pm$ 5)	5.3 ($\pm$ 5)	5.6 ($\pm$ 5)	0.80
LOS, days	10 ($\pm$ 5)	8.1 ($\pm$ 2)	11 ($\pm$ 6)	0.04
Defined EZ, no. (%)	54 (95%)	21 (100%)	33 (92%)	0.17
Complications, no. (%) [*]				0.12
None	57 (89%)	17 (81%)	40 (93%)	
Asymptomatic hemorrhage	5 (9%)	4 (19%)	1 (3%)	
Symptomatic hemorrhage	1 (1.5%)	0 (0%)	1 (3%)	
Electrode pullout	1 (1.5%)	0 (0%)	1 (3%)	

Unless otherwise indicated, values are expressed as the mean ($\pm$ SD).

^{*} Calculated using the number of implantations (64 overall, 21 for Engel I, 43 for Engel > I).

operating times almost one-third those of the frame-based approach.¹⁴ Our description in this paper demonstrates operating times that are slightly improved from our prior studies (Table 2).^{13–15} Children can present specific technical challenges with regard to their thin, squamous temporal bone. We have found that a short, orthogonal drilling trajectory is ideal for bone purchase with the bolt. Any deviation or “wiggle” within the drilling process will make it difficult to maintain the trajectory within the thin temporal bone, and the stable, robotic platform guards against this. In addition, we use bolts that are 5–10 mm longer

than standard in order to maintain the trajectory through the temporalis muscle in this region.

As we have gained more experience with SEEG, we have found that the most important aspect of defining the EZ is generating multiple, well-reasoned preoperative hypotheses. As our preimplantation hypotheses have become more refined, we have been able to place implants in patients in an individualized manner by targeting the likely networks involved. For example, a patient with a suspected focus in the frontotemporal or anterior perisylvian region will have electrodes placed in the orbitofrontal, mesial

FIG. 1. Patient flow diagram outlining the outcome for each patient included in the study.

TABLE 3. Univariate analysis of post-SEEG resective surgery: operative variables, pathology, outcomes, and follow-up in seizure-free and seizure recurrence groups

Variable	Overall, n = 42	Engel I, n = 21	Engel >I, n = 21	p Value
Mean no. of cerebral lobes resected ($\pm$ SD)	1.5 ($\pm$ 0.7)	1.3 ($\pm$ 0.5)	1.6 ($\pm$ 0.9)	0.30
Type of resections, no. (%)				1.0
Multilobar	14 (33%)	7 (33%)	7 (33%)	
Unilobar	28 (67%)	14 (67%)	14 (67%)	
Lobe of resection, no. (%)				
Frontal	21 (50%)	8 (38%)	13 (62%)	0.12
Temporal	22 (52%)	12 (57%)	10 (48%)	0.54
Parietal	8 (19%)	3 (14%)	5 (24%)	0.43
Occipital	4 (10%)	3 (14%)	1 (5%)	0.28
Central	7 (17%)	3 (14%)	4 (19%)	0.67
Pathology, no. (%)				0.05
FCD	34 (81%)	17 (81%)	17 (81%)	
Gliosis	5 (12%)	4 (19%)	1 (5%)	
No abnormality found	3 (7%)	0 (0%)	3 (14%)	
Median preop seizure frequency/mo (range)	13.5 (0.6–203)	15 (0.6–150)	15 (1–203)	0.53
Median postop seizure frequency/mo (range)	0.6 (0–215)	0 (0)	10 (0.1–215)	<0.0001
Mean follow-up time from resection, mos ($\pm$ SD)	18.4 ($\pm$ 16)	19.6 ($\pm$ 18)	17.2 ($\pm$ 13)	0.62

FCD = focal cortical dysplasia.

temporal, frontotemporal opercular, and insular regions in an orthogonal fashion. Patients in whom we particularly suspect an insular etiology, however, may have electrodes placed down the long axis of the anterior and posterior insula. Unlike in adults, in whom seizure semiology is often rich and can be described in detail, usually with better localized interictal and ictal EEG, seizures in children are often less revealing in their semiology and EEG. As a result, a comprehensive noninvasive evaluation—including ictal SPECT, FDG-PET, and MEG when possible—is particularly important in a pediatric population with a high percentage of nonlesional MR images such as the

cohort studied here. In fact, every patient had at least 1 of these supplementary studies and 46% of all of our patients underwent all 3 studies (Table 1). In our prior description of our experience in pediatric and adolescent patients, we localized a hypothetical EZ in 87% of patients, whereas this paper demonstrates that EZs in 95% of patients were presumptively localized. The 3 patients for whom we were unable to define an EZ had no seizures during their stay or had a complication necessitating removal.

On the other hand, despite being able to define an EZ in 95% of cases, our seizure freedom rate was only 50%. Why do half of our patients continue to experience seizures after having their EZ mapped and theoretically localized? Prior studies have suggested that early seizure recurrence is related to either inaccurate localization of the epileptic focus or incomplete resection.¹⁸ When examining surgical failures specifically in children, residual epileptogenic tissue near the resection cavity, a distant EZ, and a hemispheric epilepsy syndrome have been found to be the most common reasons for seizure recurrence.¹² Of the 6 patients in whom we performed a second operation, 3 of them had undergone an intentionally limited initial resection because of concerns over visual field dysfunction or for other reasons. All 3 subsequently became seizure free after undergoing the second, complete resection. The other 3 patients' initial resections were completed as guided by the SEEG. Two of these 3 patients did not improve with a subsequent resection that extended the prior initial resection. Thus, incomplete resection may account for some portion of our surgical failures but probably does not represent the majority.

The next explanation is that the EZ either was incorrectly localized or was correctly localized but was only

FIG. 2. Kaplan-Meier survival analysis of all 42 patients. Figure is available in color online only.

one of multiple EZs that were not resected and subsequently continued to seize. One of the major advances in our understanding of epilepsy has been treating it as a disease of neuronal networks. SEEG allows us to investigate each “node” in the network to try to define the epileptogenic zone. One of the most important aspects of invasive monitoring that remains elusive is refining the interpretation of the electrical data gathered through these depth electrodes. What constitutes a true onset pattern of seizure activity from a particular node versus spread from another is not always immediately apparent. To that end, we have shown that most seizures demonstrate a “fingerprint” of preictal spiking followed by multiband fast activity with concurrent suppression of lower frequencies.¹⁶ Others have demonstrated the importance of ictal baseline shifts and high-frequency oscillations in identifying seizure-onset zones.^{23,25} Future research should thus be directed at examining the seizure-onset patterns of patients who are within this surgical failure group to identify whether these failures represent either misplaced preoperative hypotheses leading to suboptimal electrode placement or a misinterpretation of what is presumed to be seizure onset but actually represents spread of ictal activity. This will be particularly helpful in patients with nonlesional epilepsy in whom the anatomical-electrical correlative SEEG data will form the basis for a surgical plan.

Very few studies have examined seizure outcomes specifically in pediatric patients undergoing SEEG. Half of our patients undergoing resective surgery remained seizure free 19 months postresection, whereas none of the patients who did not undergo surgery were seizure free. These outcomes are similar to other groups’ pediatric series,^{10,20} although it should be noted that MRI sequences in 56% of our patients were nonlesional, significantly higher than the rate reported elsewhere (14%–17%)^{10,20} and one of the main predictors of seizure outcome in meta-analyses.^{11,21,22} In our study, when we examined individual predictors of seizure outcome, whether or not the patient had a resection, older age, and shorter SEEG LOS were the only factors associated with seizure freedom when looking at the entire group. When we included these among a number of other variables in a logistic regression model, these factors remained statistically significant. A shorter LOS in the epilepsy monitoring unit probably reflects more confidence in defining the EZ, leading to improved outcomes. Interestingly, older age has been associated with improved outcomes in nonlesional extratemporal lobe epilepsy in children,³ although a more recent meta-analysis has not substantiated this finding.¹¹ This may be a reflection of the particular subset of children selected for robot-assisted SEEG. As discussed above, these patients typically had nonlesional disease and many AEDs had failed to control seizures. Younger children usually have poorly defined semiology, which is thought to reflect a less “mature” CNS³ with presumably more diffuse epileptogenic networks. Thus, it may be that older children with better-defined semiology and/or more mature epileptogenic networks were able to be better delineated with SEEG, leading to better outcomes (Fig. 3).

Similar to prior SEEG studies, the major complication seen in our implantations is hemorrhage in any of the in-

TABLE 4. Multivariate predictors of seizure outcome in all patients and patients undergoing resection

Predictors of Seizure Outcome	Value
All patients*	
Resective surgery	1.61, 10.1, $p = 0.002$
Age	0.23, 8.8, $p = 0.003$
LOS	-0.3, 6.3, $p = 0.01$
Patients undergoing resection†	
Age	0.87 (0.78–0.97), $p = 0.01$
LOS	1.16 (1.01–1.32), $p = 0.03$

* Generalized linear model including all patients scored as either Engel I or Engel > I. Values are expressed as the parameter estimate, chi-square likelihood, and p value. Whole model probability greater than chi-square was < 0.0001 .

† Cox proportional hazards model including all resective surgeries, in which number of years to seizure recurrence was used as the time to event, with Engel I outcomes censored. Values are expressed as the risk ratio (95% CI) and p value. Whole model probability greater than chi-square was 0.039.

tracranial compartments. Asymptomatic, small hemorrhages were most common and were present in 8% of our implantations, higher than in adults at our own center and in the few pediatric studies reported elsewhere.^{10,14,15,20} In addition, we had a single major complication necessitating removal of electrodes and evacuation of hematoma resulting in permanent neurological deficit, which we have previously reported.¹⁴ There are a few possibilities for the higher rate of hemorrhages in this study. The most obvious potential reason is sample size. In any single-center study in a relatively limited sample population, the observed prevalence of any particular complication will vary around the true prevalence. We have previously shown a total complication rate of 3%–4% and a symptomatic complication rate of 1% in 2 separate samples of 100 consecutive cases.^{13,14} In this study, the hemorrhagic complication rate was 9% (6/64 procedures) and symptomatic complication rate was 1.5% (1/64 procedures). Thus, because our sample size is approximately one-quarter of that combined sample, it may simply be a case of increased variance.

Another possibility includes sample bias. Unlike most centers,^{1,8,10,20} we obtain CT scans after both electrode placement and electrode removal, which increases the opportunity to detect asymptomatic hemorrhages. In fact, one of the asymptomatic bleeding events was only seen on the postremoval CT scan. One difference in terms of imaging compared to our prior studies is the use of preoperative CTA rather than intraoperative internal carotid digital subtraction angiograms. However, a prior systematic review has demonstrated no differences in complication rates between various types of vascular imaging,⁷ and the morbidity related to catheter-based angiograms must be taken into account as well. Finally, it is possible that the 1-mm entry point error typical of using robotic assistance¹⁴ may occasionally be enough to nick a cortical vessel on entry. For comparison, a recent meta-analysis of complications in subdural grid electrode placement found a pooled prevalence of 4% for intracranial hemorrhage, 5.3% for wound or neurological infections, and 2.4% for elevated intracranial pressure,⁴ so the alternative risk/benefit profile

FIG. 3. Illustrative case. A 16-year-old boy who began having seizures 4 years prior to surgery (head and eyes turn to the right side, then generalized tonic-clonic seizure occurs). Five AEDs failed to control his disease and, preoperatively, he was experiencing approximately 1 seizure per week. Ictal and interictal scalp video EEG monitoring demonstrated epileptiform activity arising mainly from the left frontotemporal region with occasional right frontotemporal sharp waves, and seizures arising from the left frontotemporal region with one arising bifrontally. Volumetric 3-T MRI demonstrated no lesion. **A:** PET scan shows diffuse cortical hypometabolism, left > right. **B:** Preimplantation map demonstrates exploratory hypotheses with according electrode implantation plan. MFG = middle frontal gyrus; operc = operculum; SMA = supplementary motor area; STG = superior temporal gyrus; Sup frontal G = superior frontal gyrus. **C:** Intraoperative images, lateral view, show a bilateral frontotemporal implantation, left > right. **D:** Ictal SEEG recording sample demonstrates ictal onset involving contacts 5 and 6 from electrode I' in the left temporal pole with subsequent frontal spread. **E:** MRI reconstruction with anatomical location of ictal onset region based on SEEG recording. The patient underwent a temporal pole and amygdala resection and remains seizure free 2 years postoperatively. Figure is available in color online only.

of other invasive monitoring techniques should always be kept in mind.

Our study is limited by its retrospective, single-center nature and the inherent selection bias present in these types of studies. In addition, our outcomes and complications may be limited by current technology in terms of both electrodes, and imaging used in SEEG. Future improvements in electrodes, such as flexible grids inserted through small burr holes or in the spacing and type of contacts used for depth electrode recording, may enable us to improve the spatial resolution of recording and for functional mapping because this is a relative weakness of SEEG. In addition, improvements in imaging may allow us to visualize more subtle abnormalities to better target lesions in the network, obtain better registration, and improve our ability to avoid small blood vessels.

Conclusions

Robot-assisted SEEG is an efficient, safe, and effective procedure for localizing the hypothetical EZ when properly planned using the noninvasive evaluation to generate appropriate exploratory hypotheses. Improvements in

technique have allowed us to further decrease operating times by using the robotic assistant, and improvements in planning have led to a definable EZ in 95% of children. Seizure outcomes remain good in the context of this patient population with medication-refractory, nonlesional disease, and the rate of symptomatic bleeding complications is still quite low at 1.5%. Advances in imaging and electroclinically defining the EZ will allow us to continue to improve our seizure freedom rates, and reduce complication rates in the future.

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Disclosures

Dr. Gonzalez-Martinez is a consultant for Zimmer Biomet. Dr. Gupta is a consultant for Eisai and Mallinckrodt. He is on the professional board for the Tuberous Sclerosis Alliance and on the editorial boards for *Epilepsy Currents* and *Pediatric Neurology*.

Author Contributions

Conception and design: Gonzalez-Martinez, McGovern. Acquisition of data: McGovern. Analysis and interpretation of data: Gonzalez-Martinez, McGovern, Pestana Knight, Gupta, Moosa, Bingaman. Drafting the article: Gonzalez-Martinez, McGovern. Critically revising the article: all authors. Reviewed submitted version of manuscript: Gonzalez-Martinez, McGovern, Pestana Knight, Gupta, Moosa. Approved the final version of the manuscript on behalf of all authors: McGovern. Statistical analysis: McGovern.

Correspondence

Jorge Gonzalez-Martinez: Epilepsy Center, Cleveland Clinic Foundation, Cleveland, OH. gonzaljl@ccf.org.