Emerging Surgical Strategies of Intractable Frontal Lobe Epilepsy with Cortical Dysplasia in Terms of Extent of Resection

Jung-Hoon Shin, M.D., Na-Young Jung, M.D., Sang-Pyo Kim, M.D., Eun-Ik Son, M.D., Ph.D.
Departments of Neurosurgery, Pathology, Dongsan Medical Center, Keimyung University School of Medicine, Daegu, Korea

Objective: Cortical dysplasia (CD) is one of the common causes of epilepsy surgery. However, surgical outcome still remains poor, especially with frontal lobe epilepsy (FLE), despite the advancement of neuroimaging techniques and expansion of surgical indications. The aim of this study was to focus on surgical strategies in terms of extent of resection to improve surgical outcome in the cases of FLE with CD.

Methods: A total of 11 patients of FLE were selected among 67 patients who were proven pathologically as CD, out of a total of 726 epilepsy surgery series since 1992. This study categorized surgical groups into three according to the extent of resection: 1) focal corticectomy, 2) regional corticectomy, and 3) partial functional lobectomy, based on the preoperative evaluation, in particular, ictal scalp EEG onset and/or intracranial recordings, and the lesions in high-resolution MRI. Surgical outcome was assessed following Engel’s classification system.

Results: Focal corticectomy was performed in 5 patients and regional corticectomy in another set of 5 patients. Only 1 patient underwent partial functional lobectomy. Types I and II CD were detected with the same frequency (45.45% each) and postoperative outcome was fully satisfactory (91%).

Conclusion: The strategy of epilepsy surgery is to focus on the different characteristics of each individual, considering the extent of real resection, which is based on the focal ictal onset consistent with neuroimaging, especially in the practical point of view of neurosurgery.

Key Words: Epilepsy surgery · Frontal lobe epilepsy · Cortical dysplasia.

INTRODUCTION

Regarding cortical dysplasia (CD), special interests were initiated by Dr. Andre Palmini’s study in 1991, issued at the Sixth International Bethel–Cleveland Clinic Epilepsy Symposium in Bielefeld, Germany, last 1995 in line with the topic of “Pediatric Epilepsy Surgery”. Furthermore, with the development of new structural and functional neuroimaging techniques, opportunities and indications for surgical intervention of CD are rapidly expanding. Therefore, CD became the most frequent (33%) etiology of pediatric epilepsy surgery according to the 2004 outcome survey of the International League Against Epilepsy (ILAE) and the third major substrate (13%) in adult epilepsy surgery patients. However, surgery for frontal lobe epilepsy (FLE) has also been reported to be associated with a high failure rate because of difficulties in localizing the epileptic zone and the presence of eloquent areas. In addition, many articles that relate malformations of cortical development (MCD) were already published usually regarding clinical and pathological characteristics, as well as surgical outcomes, but few regarding the practical aspect of the extent of resection.

For this reason, this study focused on surgical strategies in terms of the extent of resection to improve surgical outcome to meet the individual cases of FLE with CD.

MATERIALS AND METHODS

According to medical records, 11 patients of FLE were selected among 67 patients (temporal: 48, frontal: 11, parietal: 5, occipital: 3) who were proven pathologically as CD, out of a total of 726 epilepsy surgery series for 22 years since 1992. Patients who had a short follow-up period after surgery (less than 1 year) were excluded to deduce appropriate outcome.

This study’s protocols for preoperative evaluation included...
the patient's neurological and neuropsychological examination, neuroimaging to identify a substrate-related lesion, and noninvasive 24-hour video-electroencephalography (EEG) according to the international 10-20 system.

Magnetic resonance imaging (MRI) was performed for all patients to detect structural abnormalities. All patients were classified according to the image findings on the MRI. A definitive group was categorized based on common MRI findings of CD, which were approved by more than two interpreters, neurosurgeons, or neuroradiologists. A suspicious group was categorized by disagreement of interpreters because of the subtle signal intensity on fluid attenuation inversion recovery (FLAIR) images. A negative group was categorized as no specific lesion on brain MRI with consent. In addition, fluorodeoxyglucose-positron emission tomography (FDG-PET), single photon emission on computerized tomography (SPECT), and functional MRI (fMRI) were used to help decide the surgical target. Invasive intracranial monitoring with subdural grid, strip, or depth electrodes were also performed in selected cases with an EEG monitoring unit (EMU) for the purpose of the determination of the extent of resection. Intraoperative electrocorticography (ECoG) was also done for most patients. Somatosensory evoked potentials or awake surgical techniques were used case by case.

This study categorized surgical strategies into three groups according to the extent of resection based on the preparative semiology, MRI, and EEG findings (Table 1, Fig. 1). The first one is the focal corticectomy group (lesionectomy), which was categorized by definitive focal ictal onset on scalp EEG or intracranial recordings and/or visible lesion on MRI consistent with EEG findings. The second is the regional corticectomy group (additional corticectomy), which was classified as regional ictal EEG onset independently with MRI lesion. The third and final group is the partial functional lobectomy group, which was categorized by diffuse lesion in which it is hard to define the extent of resection with difficulty in covering suspicious area by intracranial monitoring or making appropriate craniotomy site for an operative approach, such as a frontal pole or basal frontal area. Other surgical techniques, such as multiple subpial transection (MST), were additionally used in selected patients. Awake surgery or functional mapping was also performed when lesion was proximal to the functionally eloquent cortex.

### Table 1. Three categories of the extent of resection based on surgical strategies

| Group                     | Condition                                                                 |
|---------------------------|---------------------------------------------------------------------------|
| Focal corticectomy        | Focal ictal EEG onset (less than 3 gyri or 3 cm or 6 electrodes contacts) and/or congruent definitive lesion on MRI |
| Regional corticectomy     | Regional ictal EEG onset (more than 3 gyri or 3 cm or 6 electrodes contacts) and/or definitive or suspicious or negative lesion on MRI |
| Partial functional lobectomy | Diffuse ictal EEG onset difficult to define extent of resection, especially frontal pole or basal frontal area |

### Table 2. Characteristics of patients who had frontal lobe epilepsy with cortical dysplasia

| No. | Sex | Age | MRI finding  | Intracranial recordings | ECoG | Surgical categories | Pathology | Outcome |
|-----|-----|-----|--------------|-------------------------|------|---------------------|-----------|---------|
| 1   | M   | 33  | Suspicious   | G/S/D                   | Yes  | RC (SF+MF)          | III       | II      |
| 2   | M   | 35  | Suspicious   | G/S                     | Yes  | RC with awake surgery (MF-premotor) | III       | I       |
| 3   | M   | 28  | Negative     | G/S                     | Yes  | RC (SF+Med)         | II        | I       |
| 4   | M   | 39  | Definitive   | No                      | Yes  | FC with awake surgery (MF-premotor) | II        | I       |
| 5   | M   | 22  | Definitive   | No                      | Yes  | RC (IF+OF)          | III (with DNET) | I       |
| 6   | M   | 19  | Suspicious   | G/S                     | Yes  | RC (SF+Med)         | III       | II      |
| 7   | M   | 13  | Definitive   | No                      | Yes  | FC (SF+MF)          | IIA       | III     |
| 8   | M   | 28  | Suspicious   | G/S                     | Yes  | PFL (FP + BF)       | IA        | I       |
| 9   | F   | 25  | Negative     | G/S                     | No   | FC (SF)             | IA        | I       |
| 10  | M   | 41  | Suspicious   | G/S                     | Yes  | FC (MF)             | IIB       | I       |
| 11  | M   | 25  | Definitive   | G/S                     | No   | FC (MF)             | IIA       | II      |

ECoG: electrocorticography, G: Grid, S: strip, D: depth electrodes, FC: focal corticectomy, RC: regional corticectomy, PFL: partial functional lobectomy, SF: superior frontal gyrus, MF: middle frontal gyrus, Med: medial frontal area, IF: inferior frontal gyrus, OF: orbitofrontal area, FP: frontal pole, BF: basal frontal area, DNET: dysembryoplastic neuroepithelial tumor
After surgery, all patients were maintained on the same antiepileptic drug regimens as before surgery and the medicine was tapered according to the patient’s condition. They were observed for at least one year and surgical outcome was assessed following Engel’s classification system.

RESULTS

General characteristics
A total of 11 patients with FLE (16% of CD) were selected for this topic and they underwent surgical management between March 1995 and June 2013. There were 10 males and 1 female, with an average age of 28 years (range 13–41 years). General characteristics are described in Table 2, 3.

Table 3. Summary of 11 patients who had cortical dysplasia with frontal lobe epilepsy

| Items            | Descriptions |
|------------------|--------------|
| Sex              | 10 males and 1 female |
| Age at operation| Average of 28 years (range 13–41) |
| MRI finding      | Definitive: 4, Suspicious: 5, Negative: 3 |
| EEG monitoring   | Scalp only: 3, Intracranial Grid/Strip: 7, Grid/Strip/Depth: 1 |
| Surgery          | Focal corticectomy: 5, Regional corticectomy: 5, Partial functional lobectomy: 1 |
| Pathology        | Classification of CD - IA: 2, IB: 3, IIA: 2, IIB: 3, IIIA: 3, IIIB: 1 |
| Outcome          | Engel classification - I: 8, II: 2, III: 1 |

MRI findings and surgical resection
MRI demonstrated definitive findings of cortical dysplasia in 4 patients (36%). In addition, 5 patients (45%) revealed a suspicious lesion, 1 patient with a subtle high signal intensity on the left superior frontal gyrus, and 4 patients with diffuse cortical atrophy or thickening on the frontal lobe. Two patients (19%) were included in the negative MR finding group.

A total of 8 patients (73%) needed preoperative evaluation with invasive intracranial monitoring like grid, strip, or depth electrodes (Fig. 2). Among them, 6 patients additionally underwent intraoperative ECoG to find the epileptic zone, whereas the other 2 patients had a single-stage operation with the help of only grid/strip. There were 3 patients (27%) in which only ECoG was used to remove the lesion because of the positive detection of focal ictal onset on scalp EEG according with MRI lesion (Fig. 3).

Regarding to surgery, 5 patients (45.45%) were included in the focal corticectomy group. The extent of resection was determined by definitive lesion on MRI combined with the regions of focal ictal EEG onset. Although one patient had a negative MR finding, he showed focal ictal onset on scalp EEG consistent with grid monitoring.

Another set of 5 patients (45.45%) underwent regional corticectomy (lesionectomy and additional corticectomy). In this group, one 22-year-old male patient received tumor removal and adjacent corticectomy on the right inferior frontal gyrus and orbitofrontal area, as well as an additional procedure called MST to block the propagation of epileptic discharge and to minimize neurologic functional loss from language cortex injury. He was diagnosed with dyssembryoplastic neuroepithelial tumor (DNET) and CD. CD was found on the cerebral cortex of peritumoral area.

Only one patient (9.1%) received partial functional lobectomy. His epileptic focus was presumed to be on the right middle frontal pole and basal frontal area. In this case, the study intended to reduce seizure frequency by disconnecting white matter of epileptic discharge.
He fortunately had no seizure attack after surgery with concurrent medication (Engel classification I).

**Pathology**

All patients were pathologically diagnosed with CD. Their diagnoses were revised by the new ILAE classification system of CD in 2011. A total of 5 patients (45.45%) were confirmed to be type I (2 patients for Ia, 3 patients for Ib) and 5 patients (45.45%) to be type II (2 patients for IIA, 3 patients for IIB). One patient (9.1%) was classified to be type IIIB because of associated DNET.

**Outcome**

They were observed for at least 1 year after surgery. A total of 8 patients (72.7%) were seizure-free or only experienced auras during the period (Engel’s classification I); 2 patients (18.2%) revealed only nocturnal seizures with significant improvement of daily quality (Engel’s classification II); and only 1 patient (9.1%) was included in class III. To conclude, this study presented much better outcomes (91%) than other studies (60–85%) of good surgical outcome: combination of Engel’s classifications I and II. Comparing with only Engel class I, this study’s patients revealed superior results (72.7%) to those (45.1%) of previous studies.

**DISCUSSION**

If a patient with intractable epilepsy who has evidence of underlying structural pathology confirmed with high-resolution MRI, the patient can be a surgical candidate. The association of the well-circumscribed lesion and good postoperative outcome has been demonstrated in many studies,9,27,28,34 because of the uncomplicated decision-making regarding surgical extent and approach. A total of 4 patients with definitive lesion in this study’s series butressed these results through excellent postoperative outcomes (Engel’s class I for 3 patients, II for 1 patient). With regard to pathology, Kabat and Król25 presented that the specific MRI feature for CD was more evident in type II than type I. They also mentioned that FCD type II is more often found in extratemporal locations with predilection toward the frontal lobe.26 Although the same frequency was detected for types I and II, a definitive MR lesion was more common for type II than type I FCD in this study’s series. Kuzniecky25 reported a correlation between the presence of hypertense areas on T2-weighted images and balloon cells, which can be found in type IIIB FCD.

For patients with negative lesion on MRI, EEG findings (on either scalp, intracranial monitoring or ECoG) can be very important contributions to epilepsy surgery. Typical MRI findings are not present in one third to one half of patients with cortical dysplasia who are undergoing epilepsy neurosurgery. Through these cases, it should be noted that imaging does not always provide adequate clinical information about the location of operation, with the structural abnormality not necessarily indicating the epileptic zone.

Then, how should the decision on the delineation of the extent of real resection take place? In the real operative situation, ECoG can be an additional option to decide the identity of the epileptic zone and the need for additional resection after initial cortical removal, and to delineate the extent of resection because the continuous ictal-like interictal epileptiform discharges were found on ECoG in the majority of patients harboring CD.20,21,26,27 At present, lesionectomy alone has produced mixed results. Some authors report favorable seizure outcomes compared with tailored cortical resections, while others report the opposite.28,29 However, several studies already revealed that the complete resection of cortical dysplastic lesion and epileptogenic areas around CD are important predictors of seizure outcome.20,22,23,29,30 Therefore, wide tailored resection can be considered a safe option to
control intractable epilepsy. This study’s protocol, the tailored resection by intraoperative recording (ECoG) and functional brain mapping techniques to identify the epileptic and eloquent areas, could be a procedural option especially for CD regarding the neurosurgeon’s role.

In addition, how much should be included in the adjacent brain tissue? The importance of complete resection indicates that seizures may originate from the periphery and the center of CD. Previous studies revealed better surgical outcomes after a wider extended resection, which exceeded the areas that revealed epileptic discharges on the ECoG.20 Regarding one case with concurrent tumor, Lee and Son27 and Seo et al.28 already reported 7 cases that had the coexistence of CD and neoplasia. They found that the surgical outcome was favorable when tumor is removed with the adjacent epileptic cortex. The same result has been verified in this study. It can be a reasonable recommendation to remove mass with the conception of a tailored resection of the peritumoral epileptic zone for brain tumor surgery.

CONCLUSION

In terms of delineation of the extent of resection, this study attempted to apply more strict indications to select the surgical candidates, such as more localized ictal EEG onset via scalp and/or intracranial electrodes consistent with more definitive MRI findings. In addition, for a more practical point of view, the final extent of resection was taken into great consideration on whether it could be expanded to the adjacent gyri according to the active interictal epileptiform discharges by the intraoperative ECoG as an adjuvant guideline more than that made by preop evaluation to remove mass with the conception of a tailored resection of the peritumoral epileptic zone for brain tumor surgery.

References
1. Awad IA, Rosenfeld J, Ahl J, Hahn JF, Lüders H: Intractable epilepsy and structural lesions of the brain: mapping, resection strategies, and seizure outcome. Epilepsia 32: 179-186, 1991
2. Barkovich AJ, Kuzniecky RI: Neuroimaging of focal malformations of cortical development. J Clin Neurophysiol 13: 481-494, 1996
3. Bautista RE, Cobbs MA, Spencer DD, Spencer SS: Prediction of surgical outcome by interictal epileptiform abnormalities during intracranial EEG monitoring in patients with extrahippocampal seizures. Epilepsia 40: 880-890, 1999
4. Becker AJ, Blümcke I, Urbach H, Hans V, Majores M: Molecular neuropathology of epilepsy-associated glioneuronal malformations. J Neuropathol Exp Neurol 65: 99-108, 2006
5. Blümcke I, Thom M, Aronica E, Armstrong DD, Vintens HV, Palmini A, et al.: The clinicopathologic spectrum of focal cortical dysplasias: a consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission. Epilepsia 52: 138-174, 2011
6. Bronen RA, Vowes RP, Kim JH, Fulbright RK, Spencer SS, Spencer DD: Focal cortical dysplasia of Taylor, balloon cell subtype: MR differentiation from low-grade tumors. AJNR Am J Neuroradiol 18: 1141-1151, 1997
7. Chassoux F, Devaux B, Landré E, Turak B, Natif F, Varlet P, et al.: Stereoelectroencephalography in focal cortical dysplasia: a 3D approach to delineating the dysplastic cortex. Brain 123 (Pt 8): 1733-1751, 2000
8. Cohen-Gadol AA, Ozbulan K, Irotten RA, Kim JH, Spencer DD: Long-term outcome after epilepsy surgery for focal cortical dysplasia. J Neurosurg 101: 55-65, 2004
9. Davies KG, Weeks RD: Cortical resections for intractable epilepsy of extratemporal origin: experience with seventeen cases over eleven years. Br J Neurosurg 7: 343-353, 1993
10. Dubeau F, Palmini A, Fish D, Avoli M, Gambardella A, Spezafico R, et al.: The significance of electrocorticographic findings in focal cortical dysplasia: a review of their clinical, electrophysiological and neurochemical characteristics. Electroencephalogr Clin Neurophysiol Suppl 48: 77-96, 1998
11. Engel J Jr, Van Ness PC, Rasmussen TB, Ojemann LM: Outcome with respect to epileptic seizures in Engel J Jr (ed): Surgical treatment of the Epilepsies, ed 2. New York: Raven Press, 1993, pp609-621
12. Englot DJ, Wang DD, Rolston JD, Shih TT, Chang EF: Rates and predictors of long-term seizure freedom after frontal lobe epilepsy surgery: a systematic review and meta-analysis. J Neurosurg 116: 1042-1048, 2012
13. Eriksson S, Malmgren K, Rydenhag B, Jonsson L, Uvebrant P, Nordborg C: Surgical treatment of epilepsy—clinical, radiological and histopathological findings in 139 children and adults. Acta Neurol Scand 99: 8-15, 1999
14. Gambardella A, Palmini A, Andermann F, Dubeau F, Da Costa JC, Quesney LF, et al.: Usefulness of focal rhythmic discharges on scalp EEG of patients with focal cortical dysplasia and intractable epilepsy. Electroencephalogr Clin Neurophysiol 98: 243-249, 1996
15. Giuliani M, Rubboli G, Marucci G, Martinoni M, Volpi L, Michelucci R, et al.: Seizure outcome of epilepsy surgery in focal epilepsies associated with temporomassal glioneuronal tumors: lesionomecomy compared with tailored resection. J Neurosurg 111: 1277-1282, 2009
16. Gump WC, Skjesi KL, Karkare SN: Seizure control after subtotal lesional resection. Neurosurg Focus 34: E1, 2013
17. Hader WJ, Mackay M, Otsuho H, Chitoku S, Weiss S, Becker L, et al.: Cortical dysplastic lesions in children with intractable epilepsy: a role of complete resection. J Neurosurg 100 (2 Suppl Pediatrics): 110-117, 2004
18. Harvey AS, Cross JH, Shinnar S, Mathern GW: ILAE Pediatric Epilepsy Surgery Survey Taskforce: Defining the spectrum of international practice in pediatric epilepsy surgery patients. Epilepsia 49: 146-155, 2008
19. Hashimzne K, Kiriyama K, Kunimoto M, Maeda T, Tanaka T, Miyamoto A, et al.: Correlation of EEG, neuroimaging and histopathology in an epilepsy patient with diffuse cortical dysplasia. Childs Nerv Syst 16: 75-79, 2000
20. Hauptman JS, Mathern GW: Surgical treatment of epilepsy associated with cortical dysplasia: 2012 update. Epilepsia 53 Suppl 4: 98-104, 2012
21. Hong SC, Kang KS, Seo DW, Hong SB, Lee M, Nam DH, et al.: Surgical treatment of intractable epilepsy accompanying cortical dysplasia. J Neurosurg 93: 766-773, 2000
22. Jobst BC, Siegel AM, Thadani VM, Roberts DW, Rhodes HC, Williamson PD: Intractable seizures of frontal lobe origin: clinical characteristics, localizing signs, and results of surgery. Epilepsia 41: 1139-1152, 2000
23. Kabat J, Krol P: Focal cortical dysplasia - review. Pol J Radiol 77: 35-43, 2012
24. Kloss S, Pieper T, Pannek H, Holthausen H, Tuckhorn I: Epilepsy surgery in children with focal cortical dysplasia (PCD): results of long-term seizure outcome. Neuropediatrics 33: 21-26, 2002
25. Kral T, Kuczaty S, Blümcke I, Urbach H, Clusmann H, Wiestler OD, et al.: Postsurgical outcome of children and adolescents with medically refractory frontal lobe epilepsies. Childs Nerv Syst 17: 595-601, 2001
26. Kuzniecky RI: Neuroimaging in pediatric epilepsy. Epilepsia 37 Suppl 1: S10-S21, 1996
27. Lee MH, Son EJ: Comparison between initial and recent surgical outcome of 15-year series of surgically remediable epilepsy. J Korean Neurossurg Soc 48: 230-235, 2010
28. Liava A, Francione S, Tassi L, Lo Russo G, Cossu M, Mai R, et al.: Individually tailored extratemporal epilepsy surgery in children: anatomo-electro-clinical features and outcome predictors in a population of 53 cases. Epilepsy Behav 25: 68-80, 2012
29. Palmini A, Andermann E, Olivier A, Tampieri D, Robitaille Y: Focal neuronal migration disorders and intractable partial epilepsy: results of surgical treatment. Ann Neurol 30: 750-757, 1991
30. Rosenow F, Lüders HO, Dinner DS, Prayson RA, Mascha E, Wolgammuth BR, et al.: Histopathological correlates of epileptogenicity as expressed by electrocorticographic spiking and seizure frequency. Epilepsia 39: 850-856, 1998
31. Seo JY, Son EJ, Yi SD, Lee CY, Lee JC, Kim DW, et al.: Coexistence of neoplasia and cortical dysplasia associated with intractable epilepsy: a clinical study of seven surgical patients and surgical strategies. J Korean Neurossurg Soc 27: 516-522, 1998
32. Sinclair DR, Wheatley M, Snyder T: Frontal lobe epilepsy in childhood. Pediatr Neurol 30: 169-176, 2004
33. Sisodiya SM: Surgery for malformations of cortical development causing epilepsy. Brain 123 (Pt 6): 1075-1091, 2000
34. Téllez-Zenteno JF, Dhar R, Wiebe S: Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis. Brain 128 (Pt 5): 1188-1198, 2005
35. Vachhrajani S, de Ribaupierre S, Otsubo H, Ochi A, Weiss SK, Donner EJ, et al.: Neurosurgical management of frontal lobe epilepsy in children. J Neurosurg Pediatr 10: 206-216, 2012
36. Weber JP, Silbergeld DL, Winn HR: Surgical resection of epileptogenic cortex associated with structural lesions. Neurosurg Clin N Am 4: 327-336, 1993