There is inherent difficulty in identifying the epileptogenic zone in nonlesional neocortical epilepsy, which leads to the incomplete resection. However, with careful interpretation of other studies including functional neuroimaging and the presence of concordant results, surgical treatment can benefit selected patients with nonlesional neocortical epilepsy. Two recent large studies including ours demonstrated that seizure free outcomes were 47 and 55% for nonlesional TLE, and 41 and 43% for nonlesional extratemporal lobe epilepsy patients. Concordance with two or more presurgical evaluations among interictal EEG, ictal EEG, FDG-PET, and ictal SPECT was significantly related to a seizure-free outcome. However, we should be cautious to the possibility of false localization of ictal EEG or functional neuroimaging in nonlesional neocortical epilepsy. Careful placement of intracranial electrodes on the presumed epileptogenic zone and the adjacent areas should be needed for these patients. The repositioning of intracranial electrodes after the failure in identifying ictal onset zone at the initial intracranial study might identify a new ictal onset zone. Consideration of one-week interval repositioning of intracranial electrodes could be helpful in selected patients. Intracranial EEG is one of the most important procedures in planning surgery and achieving a good surgical outcome in resective epilepsy surgery. Slow propagation and focal or regional ictal onset rather than widespread onset were associated with a seizure-free outcome. Complete resection including the area with initial three second ictal rhythm and interictal abnormalities predicts a good surgical outcome. 

Key words: Epilepsy surgery; Nonlesion; Neocortical

Introduction

Neocortical epilepsy has comprised only a minor portion of epilepsy surgical series until now.1 It has not homogenous clinical manifestations. Widely different seizure semiologies could be found depending on the location of the epileptogenic foci. We do not know clearly the characteristics of epileptogenic network of these patients. Scalp EEG often misleads or falsely localizes the ictal onset zone due to inaccessible location or widespread ictal onset.

A focal structural lesion on MRI is a reliable indicator of the seizure onset.2-4 Concordance of electrophysiological studies and MRI findings has high predictive value for good surgical outcome.5,6 However, MRI is ineffective in many partial epilepsy patients, even patients with cortical dysplasia. Multimodal evaluations are mandatory for the successful epilepsy surgery in these patients. Intracranial recording is also indispensable role for these patients. Surgical outcome has usually been known to be less well satisfactory.1,7,8 In the context of all these issues, determining the prognostic factors for good surgical outcome and suggesting the guideline of successful epilepsy surgery are very important for the this special group of patients.

Surgical outcome and prognostic factors in neocortical epilepsy surgery

Extratemporal resections are known to be generally less successful than are temporal lobe resections. By multivariate analysis, the median proportion of long-term seizure-free patients (more than five years) was 66% with temporal lobe epilepsy (TLE), 46% with occipital and parietal lobe epilepsies (OLE and PLE), and 27% with frontal lobe epilepsy (FLE).9 However, the recent series suggested that many neocortical epilepsy patients are likely to benefit from surgical treatment, and 57.5% became seizure free more than two years after surgery (41.0% in FLE, 71.2% in
neocortical TLE, 57.5% in PLE, and 68.1% in OLE). It has been a consistent finding that the presence of focal MRI lesion indicated good surgical outcome in epilepsy surgery including temporal and extratemporal lobe epilepsies. The seizure free rate ranged from 20 to 50% in nonlesional epilepsy depending on the lobes (Table 1). However, the seizure rate increased up to 55 to 70% in lesional cases. A meta-analysis to assess predictors of epilepsy surgery found out that a good outcome was related with presence of febrile convulsion, mesial temporal sclerosis, tumors, abnormal MRI, EEG/MRI concordance, and extensive surgical resection. The resection of an epileptogenic lesion with an ictal onset zone is recognized as the most important factor for a good surgical outcome. The majority of surgical series suggested that the identification of a specific lesion usually leads to a favorable outcome.

Our recent study using multivariate analysis of a large series of patients also showed that a focal lesion on MRI, focal hypometabolism on PET, and localized ictal onset on EEG were independent significant positive prognostic factors. In another large series of FLE, MRI-negative malformation of cortical development, any extrafrontal MRI abnormality, generalized/non-localized ictal EEG patterns, occurrence of acute post-operative seizures, and incomplete surgical resection were correlated with poor surgical outcome.

MRI is also an important factor to make the patients have epilepsy surgery after presurgical evaluations. Up to 30% of patients who underwent presurgical evaluations for respective surgery ultimately did not have this form of surgery. Localized MRI abnormality and consistently localized EEG findings were most strongly associated with leading to surgery.

### Surgical outcome and prognostic factors of nonlesional neocortical epilepsy

There is inherent difficulty in identifying the epileptogenic zone in nonlesional neocortical epilepsy, which leads to the incomplete resection. Until recently, only a minority of patients have been known to be seizure free after the resection. However, the seizure free rate of the patients even with normal MRI who underwent surgery was significantly superior to that of the patients who did not have surgery. Seizure free outcome ranged from 31 to 70% for nonlesional temporal lobe epilepsy, and from 17% to 57% for extratemporal nonlesional epilepsy (Table 2). Two recent large studies including ours demonstrated that seizure free outcomes were 47 and 55% for nonlesional TLE, and 41 and 43% for nonlesional extratemporal lobe epilepsy patients. Our study also showed that localization by FDG-PET or interictal EEG was correlated with a seizure-free outcome. Concordance with two or more presurgical evaluations among interictal EEG, ictal EEG, FDG-PET, and ictal SPECT was significantly related to a seizure-free outcome. As for long-term outcome of patients with MRI negative TLE, only non-congruent FDG-PET results could be identified to be associated with poor surgical outcome. In another study with the TLE patients with normal MRI, the absence of contralateral or extratemporal interictal spikes and concordant subtraction ictal SPECT were associated with good surgical outcome. With careful interpretation of other studies including functional neuroimaging and the presence of concordant results, surgical treatment can benefit selected patients with nonlesional neocortical epilepsy.

### Table 1. Surgical outcome related with the presence of lesion on MRI.

| Sites          | Author                  | Percent of seizure free rate (n=number of patients) |
|----------------|-------------------------|-----------------------------------------------------|
|                |                         | No lesion on MRI | Focal lesion on MRI          |
| All lobes      | Spencer, et al.          | 43% (n=43)       | 70% (n=183)                  |
|                | Guldvog, et al.          | 45% (n=33)       | 57% (n=47)                   |
|                | Yun, et al.              | 62% (n=111)      | 40% (n=82)                   |
| TLE            | Berkovic, et al.         | 33% (n=21)       | 65% (n=86)                   |
|                | Guldvog, et al.          | 50% (n=26)       | 59% (n=27)                   |
| Extra-temporal | Zetner, et al.           | 20% (n=10)       | 61% (n=46)                   |
|                | Guldvog, et al.          | 29% (n=7)        | 55% (n=20)                   |
| FLE            | Smith, et al.            | 29% (n=17)       | 66% (n=32)                   |

TLE, temporal lobe epilepsy; FLE, frontal lobe epilepsy.
*All patients had neocortical epilepsies including neocortical temporal and extratemporal lobe epilepsies.
**Table 2.** Surgical outcome of nonlesion epilepsy. The results of various studies

| Author       | Lobes   | Number of patients | Engel classification |
|--------------|---------|--------------------|----------------------|
|              |         |                    | I  | II | III | IV  |
| Siegel, et al.19 | TLE    | 10                 | 70%| 20%| 10% |      |
|               | Extra TLE | 14              | 57%| 21%| 21% |      |
| Blume, et al.20 | TLE    | 43                 | 42%| 19%| 14%| 26%  |
|               | Extra TLE | 27               | 30%| 4% | 7% | 59%  |
| Chapman, et al.21 | TLE  | 13                 | 31%| 54%| 15%|      |
|               | Extra TLE | 11               | 45%| 20%|      | 35%  |
| Alacron, et al.22 | TLE  | 13                 | 62%| 31%| 8%| 0%   |
|               | Extra TLE | 6               | 17%| 17%| 33%| 33%  |
| Jayakar, et al.23 | TLE   | 47                 | 47%| 15%| 17%| 21%  |
|               | Extra TLE | 54             | 41%| 15%| 28%|      |
| Lee, et al.24  | TLE    | 31                 | 55%| 10%| 16%| 19%  |
|               | Extra TLE | 58             | 43%| 5% | 31%| 21%  |

**False localization of functional neuroimaging**

Ictal SPECT and FDG-PET can be critical for localizing the seizure focus, especially in nonlesional patients. However, we should consider the possibility of false localization. We analyzed 33 consecutive patients with nonlesional neocortical epilepsy who had a scalp ictal onset zone localized in the temporal lobe and good surgical outcome after focal neocortical resection.27 Epileptogenic zone outside the temporal lobe was not infrequently encountered in the patients who were diagnosed as non-lesional lateral temporal lobe epilepsy on long-term scalp video-EEG monitoring. Some studies demonstrated that FDG-PET and subtraction SPECT were valuable in the diagnosis of non-lesional neocortical epilepsy.28-33 However, in the patients with intracranial ictal zones outside the temporal lobe, their values were limited. FDG-PET and subtraction SPECT had localizing value in no more than half of patients, which even showed false localizations occasionally. Careful placement of intracranial electrodes on the presumed epileptogenic zone and adjacent areas should be needed for these patients.

**Repositioning of intracranial electrodes**

Accurate localization of ictal onset zone by intracranial electrodes is one of the most sensitive and important method in the success of epilepsy surgery.34-37 In the presurgical evaluation of non-lesional neocortical epilepsy, intracranial monitoring is indispensable but has the limitation of the possibility of insufficient sampling. One recent study showed that stereo-EEG was equally effective in the presurgical evaluation of both MRI-negative and lesional epilepsies.38 To get the appropriate information from intracranial monitoring, many intracranial electrodes may be needed. Nevertheless, because these electrodes cover only limited portion of brain, the true ictal onset zone can sometimes be missed29-41 and sometimes the repositioning or additional electrode can be needed. To avoid missing true ictal onset zone, it is important to make strong hypothesis derived from congruent results of presurgical evaluation.

Sometimes, the repositioning or adding intracranial electrodes is helpful to find the true ictal onset zone after the failure of identifying it at the initial evaluation. Our group recruited 18 cases underwent a second invasive study consisting of repositioning or additional implantation of intracranial electrodes performed a week after the initial invasive study.42 The repositioning of intracranial electrodes identified a new ictal onset zone in 13 patients. In another four cases the second evaluation made the change of decision on the resection margin. Seven of 11 patients who were ultimately found to have focal ictal onset zone by the second evaluation became seizure free after the operation. The spatial restriction of ictal rhythm is the important predictor for good surgical outcome. These results support consideration of one-week interval repositioning of intracranial electrodes in selected patients.
Decision of extent based on the results of invasive study

The objectives of intracranial EEG are to define interictal abnormalities and the ictal onset zone, and to map the cortical function. Based on these results, physicians can determine the extent of the surgical resection. The surgical outcome depends strongly on the identification and complete resection of a well-defined epileptogenic zone. Therefore, the extent of the resection may contribute to the surgical outcome. Intracranial EEGs were analyzed in 177 consecutive patients who had undergone resective epileptic surgery. Based on the results of invasive evaluations, slow propagation and focal or regional ictal onset were associated with a seizure-free outcome. A seizure-free outcome was significantly associated with a resection that included the area showing ictal spreading rhythm during the first three seconds or included all the electrodes showing pathological delta waves or frequent interictal spikes more than 0.2 Hz.

Conclusions

Surgical treatment can benefit selected patients with non-lesional neocortical epilepsy. Presurgical evaluations other than MRI including functional neuroimagings can correctly localize the epileptogenic lobe in these patients. Concordance of presurgical evaluations is important for successful epilepsy surgery. We should know the usefulness and limitations of various presurgical diagnostic modalities and their meanings in combination including intracranial EEGs. The strength of hypothesis based on the results of non-invasive evaluation is a key to successful epilepsy surgery for these patients.

References

1. Zetener J, Hufnagel A, Ostertum B, et al. Surgical treatment of extratemporal epilepsy: clinical, radiologic, and histopathologic findings in 60 patients. *Epilepsia* 1996;37:1072-80.
2. Radhakrishnan K, So EL, Silbert PL, et al. Predictors of outcome of anterior temporal lobectomy for intractable epilepsy: a multivariate study. *Neurology* 1998;51:465-71.
3. Cacino GD. Surgical treatment for extratemporal epilepsy. *Curr Treat Options Neurol* 2004;6:257-62.
4. Mosewich RK, So EL, O'Brien TJ, et al. Factors predictive of the outcome of frontal lobe epilepsy surgery. *Epilepsia* 2004;41:843-9.
5. Bronen RA. Epilepsy: the role of MR imaging. *Am J Radiol* 1992;159:1165-74.
6. Cascino GD, Boon PA, Fish DR. Surgically remediable lesional syndrome. In Engel J Jr, ed. *Surgical Treatment of the Epilepsies*: 2nd ed. New York: Raven Press, 1993:77-86.
7. Haglund MM, Ojemann GA. Extratemporal respective surgery for epilepsy. *Neurosurg Clin North Am* 1993;4:283-92.
8. Talairach J, Bancaud J, Boris A, et al. Surgical therapy of frontal epilepsies. *Adv Neurol* 1992;57:702-32.
9. Tellez-Zeteno J, Dhar R, Wiebe S. Long-term seizure outcomes following epilepsy surgery: a systemic review and meta-analysis. *Brain* 2005;128:1188-98.
10. Yun CH, Les SK, Lee SY, et al. Prognostic factors in neocortical epilepsy surgery: multivariate analysis. *Epilepsia* 2006;47:574-9.
11. Spencer SS. Long-term outcome after epilepsy surgery. *Epilepsia* 1996;37:807-13.
12. Guldevog B, Loyning Y, Hauglie-Hansen E, Flood S, Bjornase H. Predictive factors for success in surgical treatment for partial epilepsy: a multivariate analysis. *Epilepsia* 1994;35:566-78.
13. Berkovic SF, McIntosh AM, Kalnins RM, et al. Preoperative MRI predicts outcome of temporal lobectomy: an actuarial analysis. *Neurology* 1995;45:1358-63.
14. Smith JR, Lee MR, King DW et al. Results of lesional vs. nonlesional frontal lobe epilepsy surgery. *Stereotact Funct Neurosurg* 1997;69:202-9.
15. Tonini C, Beghi E, Berg AT, et al. Predictors of epilepsy surgery outcome: a meta-analysis. *Epilepsy Res* 2004;62:75-87.
16. Jeha LE, Najm I, Bingaman W, Dinner D, Widdess-Walsh P, Luders H. Surgical outcome and prognostic factors of frontal lobe epilepsy surgery. *Brain* 2007;130:574-84.
17. Berg AT, Vickrey BG, Langfit JT. The multicenter study of epilepsy surgery: recruitment and selection for surgery. *Epilepsia* 2003;44:1425-33.
18. Bien CG, Szinay M, Wagner J, Clusmann H, Becker AJ, Urbach H. Characteristics and surgical outcomes of patients with refractory magnetic resonance imaging-negative epilepsies. *Arch Neurol* 2009;66:1491-9.
19. Siegel AM, Jobst BC, Thadani VM, et al. Medically intractable, localization-related epilepsy with normal MRI: presurgical evaluation and surgical outcome in 43 patients. *Epilepsia* 2001;42:883-8.
20. Blume WT, Ganapathy GR, Munoz D, et al. Indices of resective surgery effectiveness for intractable nonlesional frontal epilepsy. *Epilepsia* 2004;45:46-53.
21. Chapman K, Wyllie E, Najm I, et al. Seizure outcome after epilepsy surgery in patients with normal preoperative MRI. *J Neurol Neurosurg Psychiatry* 2005;76:710-3.
22. Alarcon G, Valentín A, Watt C, et al. Is it worth pursuing surgery for epilepsy in patients with normal neuroimaging? *J Neurol Neurosurg Psychiatry* 2006;77:474-80.
23. Jayakar P, Dunoyer C, Dean P, et al. Epilepsy surgery in patients with normal or nonfocal MRI scans: integrative strategies offer long-term seizure relief. *Epilepsia* 2008;49:758-64.

Copyright © 2011 Korean Epilepsy Society
24. Lee SK, Lee SY, Kim KK, et al. Surgical outcome and prognostic factors of cryptogenic neocortical epilepsy. Ann Neurol 2005;58:525-32.
25. Immonen A, Julita L, Muraja-Murro A, et al. Long-term epilepsy surgery outcomes in patients with MRI-negative temporal lobe epilepsy. Epilepsia 2010;51:2260-9.
26. Mell ML, Rao S, So EL. Epilepsy surgery outcomes in temporal lobe epilepsy with a normal MRI. Epilepsia 2009;50:2053-60.
27. Lee SK, Yun CH, Ph JB, et al. Intracranial ictal onset zone in nonlesional lateral temporal lobe epilepsy on scalp ictal EEG. Neurology 2003;61:757-64.
28. Williamson PD, Spencer DO, Spencer SS, Novelly RA, Mattson RH. Complex partial seizures of frontal lobe origin. Ann Neurol 1985;18:497-504.
29. Geier S, Bancaud J, Talairach J, Bonis A, Szikla G, Enjelvin M. The seizures of frontal lobe epilepsy. Neurology 1977;27:951-8.
30. Henry TR, Babb TL, Engel J Jr, Mazziotta JC, Phelps ME, Crandall PM. Hippocampal neuronal loss and regional hypometabolism in temporal lobe epilepsy. Ann Neurol 1994;36:925-7.
31. Chugani HT, Shewmon DA, Shields WD, et al. Surgery for intractable infantile spasms: neuroimaging perspectives. Epilepsia 1993;34:764-71.
32. Shields WD, Duchovny MS, Holmes GL. Surgically remediable syndromes of infancy and early childhood. In: Engel J Jr, ed. Surgical Treatment of the Epilepsies, 2nd ed. New York: Raven Press, 1993:35-48.
33. Duncan R, Biraben A, Patterson J, et al. Ictal single photon emission computed tomography in occipital lobe seizures. Epilepsia 1997;38:839-43.
34. So NK. Depth electrode studies in mesiotemporal epilepsy. In: Luders H, ed. Epilepsy surgery. New York: Raven Press, 1992:371-84.
35. Spencer SS, So NK. Engel J Jr, Williamson PD, Levesque Mf, Spencer DD. Depth electrodes. In: Engel J Jr, ed. Surgical Treatment of the Epilepsies. New York: Raven Press, 1993:359-76.
36. Arroyo S, Lesser RP, Goldring S, Sutherling WW, Resnick TJ. Subdural and epidural grids and strips. In: Engel J Jr, ed. Surgical Treatment of the Epilepsies. New York: Raven Press, 1993:377-86.
37. Wylar AR, Ojemann GA, Lettich E, Ward AA Jr. Subdural strip electrodes for localizing epileptogenic foci. J Neurosurg 1984;60:1195-200.
38. McGonigal A, Bartolomei F, Regis J, et al. Stereoelectroencephalography in presurgical assessment of MRI-negative epilepsy. Brain 2007;130:3169-83.
39. Spencer SS, Spencer DD, Williamson PD, Mattson RH. The localization value of depth electroencephalography in 32 refractory epileptic patients. Ann Neurol 1982;12:248-53.
40. Spencer SS, Guimarães P, Katz A, Kim J, Spencer DD. Morphological patterns of seizures recorded intracranially. Epilepsia 1992;33:537-45.
41. Spencer SS, Lamoureux D. Invasive electroencephalography evaluation for epilepsy surgery. In: Shorvon S, Dreifuss F, Fish D, Eihomas D, ed. The Treatment of Epilepsy. Oxford: Blackwell Science, 1996:562-88.
42. Lee SK, Kim KK, Nam H, et al. Adding or repositioning intracranial electrodes during presurgical assessment of neocortical epilepsy: electrographic seizure pattern and surgical outcome. J Neurosurg 2004;100:463-71.
43. Widdess-Walsh P, Jeha L, Nair D, Kotagal P, Bingaman W, Najm I. Subdural electrode analysis in focal cortical dysplasia: predictors of surgical outcome. Neurology 2007;69:660-7.
44. Kim DW, Kim HK, Lee SK, et al. Extent of neocortical resection and surgical outcome of epilepsy: intracranial EEG analysis. Epilepsia 2010;51:1010-7.