

Role of subdural electrocorticography in prediction of long-term seizure outcome in epilepsy surgery

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Since prediction of long-term seizure outcome using preoperative diagnostic modalities remains suboptimal in epilepsy surgery, we evaluated whether interictal spike frequency measures obtained from extraoperative subdural electrocorticography (ECoG) recording could predict long-term seizure outcome. This study included 61 young patients (age 0.4–23.0 years), who underwent extraoperative ECoG recording prior to cortical resection for alleviation of uncontrolled focal seizures. Patient age, frequency of preoperative seizures, neuroimaging findings, ictal and interictal ECoG measures were preoperatively obtained. The seizure outcome was prospectively measured [follow-up period: 2.5–6.4 years (mean 4.6 years)]. Univariate and multivariate logistic regression analyses determined how well preoperative demographic and diagnostic measures predicted long-term seizure outcome. Following the initial cortical resection, Engel Class I, II, III and IV outcomes were noted in 35, 6, 12 and 7 patients, respectively. One child died due to disseminated intravascular coagulation associated with pseudomonas sepsis 2 days after surgery. Univariate regression analyses revealed that incomplete removal of seizure onset zone, higher interictal spike-frequency in the preserved cortex and incomplete removal of cortical abnormalities on neuroimaging were associated with a greater risk of failing to obtain Class I outcome. Multivariate logistic regression analysis revealed that incomplete removal of seizure onset zone was the only independent predictor of failure to obtain Class I outcome. The goodness of regression model fit and the predictive ability of regression model were greatest in the full regression model incorporating both ictal and interictal measures [R^2 0.44; Area under the receiver operating characteristic (ROC) curve: 0.81], slightly smaller in the reduced model incorporating ictal but not interictal measures (R^2 0.40; Area under the ROC curve: 0.79) and slightly smaller again in the reduced model incorporating interictal but not ictal measures (R^2 0.27; Area under the ROC curve: 0.77). Seizure onset zone and interictal spike frequency measures on subdural ECoG recording may both be useful in predicting the long-term seizure outcome of epilepsy surgery. Yet, the additive clinical impact of interictal spike frequency measures to predict long-term surgical outcome may be modest in the presence of ictal ECoG and neuroimaging data.

Keywords: clinical neurophysiology; paediatric epilepsy surgery; intracranial electroencephalography (EEG); irritative zone

Abbreviations: ECoG = electrocorticography; FDG = 2-deoxy-2-[^{18}F] fluoro-D-glucose; ROC = receiver operating characteristic; PET = positron emission tomography

Introduction

The general principle of epilepsy surgery is to remove the presumed epileptogenic zone while preserving eloquent cortex in patients with medically-uncontrolled focal epilepsy (Lüders *et al.*, 1993). To determine the extent of the presumed epileptogenic zone or the extent of eloquent cortex, extraoperative electrocorticography (ECoG) following subdural electrode placement is often employed prior to cortical resection in both paediatric and adult epilepsy centres (Rydenhag and Silander, 2001; Spencer *et al.*, 2005; Cross *et al.*, 2006; Pondal-Sordo *et al.*, 2006). Although ECoG recording using subdural electrodes suffers from an unavoidable risk of sampling errors, the seizure onset zone identified by visual assessment has empirically been considered to be one of the most important ECoG measures indicating the location of the epileptogenic zone (Rosenow and Lüders, 2001); failure to completely remove the seizure onset zone on ECoG has been considered to be a risk factor for surgical failure (Cohen-Gadol *et al.*, 2004; Jeha *et al.*, 2007; Jayakar *et al.*, 2008). The seizure onset zone can be determined only after a seizure occurs; thus, some patients may have to undergo extraoperative ECoG recording for more than a week until a seizure occurs. Such a lengthy recording period may increase the risk of complications such as infection and the medical cost related to epilepsy surgery (Hamer *et al.*, 2002; Onal *et al.*, 2003).

On the other hand, interictal ECoG recording is far easier to obtain compared with ictal ECoG recording. Interictal recording provides useful measures to predict the location of the seizure onset zone; indeed, previous studies have suggested that the cortical area showing frequent interictal spike activity often turns out to be a part of the seizure onset zone (Hufnagel *et al.*, 2000; Asano *et al.*, 2003; Widdess-Walsh *et al.*, 2007). Yet, it still remains unknown how well interictal spike frequency on subdural ECoG recording can itself predict long-term seizure outcome. It also remains unknown how well outcome-prediction can be improved by adding spike frequency measures to the other conventionally available diagnostic measures such as ictal ECoG and neuroimaging data. Here, we have addressed these two questions, using quantitative assessment of interictal spike frequency on ECoG recording.

Methods

Patients

We studied a consecutive series of 61 young patients with medically-refractory focal epilepsy (age 0.4–23.0 years; 34 males), who underwent epilepsy surgery from April 2002 to April 2006 and met the following inclusion and exclusion criteria. The inclusion criteria used in the present study included: (i) focal seizures with or without secondarily generalized tonic-clonic seizures or epileptic spasms; (ii) seizures uncontrolled despite at least two antiepileptic drugs; (iii) two-stage curative (i.e. not palliative) epilepsy surgery consisting of subdural electrode placement and cortical resection performed by a single neurosurgeon (S.S.) in Children's Hospital of Michigan in Detroit; and (iv) extraoperative ECoG recorded using the same Digital EEG System with an automatic spike detection program (Gotman and Gloor, 1976).

The exclusion criteria included: (i) one-stage epilepsy surgery without extraoperative ECoG recording (such as standard temporal lobectomy for patients with hippocampal sclerosis, lesionectomy of tumour located distant from eloquent cortex and hemispherectomy for patients with preoperative hemiparesis); (ii) the presence of bilateral independent epileptogenic foci documented according to the Phase-I presurgical evaluation (Asano *et al.*, 2001) including seizure semiology, scalp-EEG findings and neuroimaging findings; (iii) palliative surgical procedure by corpus callosotomy; (iv) neurodegenerative or metabolic disorders; and (v) high-grade brain tumour suspected by preoperative MRI. The study was approved by the Institutional Review Board at Wayne State University, and written informed consent was obtained from the parents or guardians of all subjects.

Subdural electrode placement

Placement of intracranial electrodes was guided by the results of Phase-I presurgical evaluation including: scalp video-EEG recording, MRI and 2-deoxy-2-[¹⁸F] fluoro-D-glucose (FDG) positron emission tomography (PET). Each diagnostic modality was first reviewed by investigators being blinded to the results of the other modalities. The final location and extent of subdural electrodes were then determined at a weekly comprehensive epilepsy surgery conference where all the localization findings were presented and discussed until a consensus was reached (Asano *et al.*, 2001).

For extraoperative video-ECoG recording, platinum grid electrodes (10 mm inter-contact distance; 4 mm diameter; Ad-tech, Racine, WI, USA) were surgically implanted on the presumed epileptogenic hemisphere. Subdural strip electrodes were placed in the medial temporal region and medial frontal-parietal region, if indicated by any of the above-mentioned diagnostic modalities. The lateral portion of pre- and post-central gyri was also covered with electrodes for subsequent functional mapping. Prior to dural closure, a 10-min intraoperative ECoG recording was obtained as previously described (Asano *et al.*, 2004); additional subdural electrodes were placed to reduce the risk of sampling errors if frequent interictal spike activity predominantly involved the edge of subdural grid electrode arrays. All electrode plates were stitched to adjacent plates and/or the edge of the dura mater to avoid movement, as previously described (Asano *et al.*, 2007). In addition, intraoperative photographs were obtained with a digital camera before dural closure to enhance the spatial accuracy of electrode display on the three dimensional brain surface reconstructed from MRI (Asano *et al.*, 2007). The total number of electrode contacts per patient ranged from 50 to 128.

Determination of the seizure onset zone on extraoperative ECoG recording

The ictal ECoG measures of interest in the present study included: (i) whether or not ictal events were captured during extraoperative ECoG recording; and (ii) completeness of removal of the seizure onset zone on extraoperative ECoG recording. Extraoperative ECoG recordings were obtained using a 128-channel Stellate Harmonie 5.2 Digital System (sampling rate: 200 Hz; Stellate Inc., Quebec, Canada) for 2–14 days. Anti-epileptic medications were withheld or reduced until a sufficient number of habitual seizures were captured. Ictal ECoG recordings during extraoperative monitoring were visually reviewed in the referential and bipolar montages by two electroencephalographers (Asano *et al.*, 2004, 2005b), who reached a consensus for each electrode to determine whether it should be classified as being part of the seizure onset zone. Seizure onset was defined as a sustained

rhythmic change on ECoG accompanied by subsequent clinically typical seizure activity, not explained by state changes, and clearly distinguished from background ECoG and interictal activity (Gotman *et al.*, 1993; Lee *et al.*, 2000; Asano *et al.*, 2003). Sustained rhythmic fast wave bursts at β or γ range showing subsequent morphological or spatial evolution were also considered as seizure discharges (Asano *et al.*, 2005a; Kobayashi *et al.*, 2006) when associated clinical changes were subtle or minimal, but such activities on ECoG could not be explained by physiological activities or artefacts. Brief bursts of spikes and periodic spikes at a frequency of <2 Hz prior to seizures were not considered a part of seizure onset in the present study, as this approach was applied in previous studies (Lee *et al.*, 2000; Asano *et al.*, 2003); in cases with this type of initial ECoG changes, we defined the seizure onset sites based on the subsequently evolving rhythmic discharge (Lee *et al.*, 2000; Asano *et al.*, 2003).

Quantitative measurement of interictal spike frequency on extraoperative ECoG recording

The interictal ECoG measures of interest in the present study included: (i) the frequency of interictal spikes (unit: min^{-1}) measured at the single electrode site showing the maximal spike frequency among the whole subdural electrode arrays; and (ii) the frequency of interictal spikes (unit: min^{-1}) measured at the single electrode site showing the maximal spike frequency among the surgically preserved sites. The detailed methodology to measure interictal spike frequency on subdural ECoG recording has previously been reported (Gotman and Gloor, 1976; Asano *et al.*, 2003, 2007).

In short, three distinct 10-min ECoG segments during quiet wakefulness were selected from the video-ECoG data, based on the following criteria: at least a 3-h interval between each segment; at least 8 h after a secondarily generalized tonic-clonic seizure and at least 2 h after other types of clinical seizures (Asano *et al.*, 2003). We have validated this approach and have shown high agreement in spike frequency pattern among the three 10-min segments in a separate group of children (Asano *et al.*, 2003). In cases, where very frequent interictal spikes (>30 spikes/min in an electrode) were seen and spike distribution visually appeared consistent, three distinct 5-min segments instead of 10-min segments were selected (Asano *et al.*, 2007). Subsequently, the averaged spike frequency (unit: min^{-1}) for each subdural electrode was obtained from the three ECoG segments. In cases, where extremely frequent interictal spikes (a total of 5000 spikes across the electrode arrays or 500 spikes in an electrode) were seen and spike distribution visually appeared consistent among three segments, a spike frequency for a single ECoG segment instead of three distinct ECoG segments was utilized for subsequent analyses (Asano *et al.*, 2007).

Quantitative analysis of interictal spike frequency was performed on the ECoG, using Stellate SENSE software, as previously described and validated (Gotman and Gloor, 1976; Asano *et al.*, 2003). The spike detection procedure was applied to ECoG data in the reference montage. If the extracranial reference at the contralateral mastoid was artefactual, the common average montage was used as reference (Crone *et al.*, 2001; Fukuda *et al.*, 2008). The results of the automatic detection procedure were visually reviewed, since it has been reported that none of the spike-detection methods is absolutely fail-safe and all methods require human validation (Gotman, 1999). False positive spikes (Sperling, 2003) such as movement artefacts, background fluctuation, μ -rhythm and lambda wave were removed as previously validated (Asano *et al.*, 2003). Conversely, we recognized that the

automatic spike detection program missed true spikes when they occurred after long-lasting high amplitude polymorphic slow wave activity or a cluster of spike-wave activity, since the software assumes the presence of normal background in a 5-s segment immediately preceding the analysed spike. In these cases, we visually counted and added all non-detected spikes if their amplitudes were similar or higher compared to adjacent spikes that were detected (Asano *et al.*, 2003). Subsequently, the software summed all confirmed spikes in each individual subdural electrode channel.

Neuroimaging protocol

MRI including a T_1 -weighted spoiled gradient echo image and fluid-attenuated inversion recovery image were obtained prior to placement of subdural electrodes. FDG PET studies were performed prior to placement of subdural electrodes as previously described (Lee *et al.*, 2001); the scalp EEG was monitored throughout all PET examinations.

In order to create a 3D surface image with the accurate location of electrodes as directly defined on the brain surface, planar X-ray images (lateral and anterior-posterior images) were acquired following placement of subdural electrodes; three metallic fiducial markers were placed at anatomically well-defined locations on the patient's head for co-registration of the X-ray with the MRI as previously described (von Stockhausen *et al.*, 1997; Muzik *et al.*, 2007; Juhász *et al.*, 2009). This approach allowed us to determine the spatial relationship between the extent of cortical removal, cortical abnormalities on neuroimaging and seizure onset zones.

Neuroimaging measures of interest in the present study included: (i) the presence or absence of a tumour seen on MRI; (ii) the presence or absence of any cortical lesions visible on MRI; and (iii) completeness of removal of 'cortical abnormalities on neuroimaging'. Here, 'cortical abnormalities on neuroimaging' were defined as all cortical lesions on MRI, and also defined as all cortical areas with $>15\%$ relative hypometabolism compared with the homotopic region in patients without cortical abnormalities on MRI. Thus, increased signals in the white matter area on fluid-attenuated inversion recovery MR images were not considered as a part of 'cortical abnormalities on neuroimaging'. Previous PET studies (Theodore *et al.*, 1988; Gaillard *et al.*, 2002) suggested that the incidence of 15% relative hypometabolism compared with the homotopic region was extremely rare in healthy young individuals. Determination of the optimal cutoff threshold of PET measures to obtain the best neurophysiological correlates was not a purpose of the present study. Definition of significant glucose hypometabolism using a statistical parametric mapping approach was not tenable due to the age range of patients (Muzik *et al.*, 2000).

Cortical resection following extraoperative ECoG recording

Cortical resection was guided mainly by ictal and interictal extraoperative ECoG, as well as neuroimaging data. We generally intended to remove all of the seizure onset zones in most of the patients. When the seizure onset zones were close to or within the eloquent cortex such as the primary sensorimotor area, the extent of cortical resection was determined after the epilepsy surgery team and the family of the patient had extensive discussions regarding the pros and cons of surgical resection of such areas. If ictal events were not captured, cortical resection was performed according to interictal ECoG data and the findings of other diagnostic modalities. We generally intended to remove all cortical abnormalities on neuroimaging, unless such multiple neuroimaging abnormalities were located in areas distant from the

seizure onset zone or in the contralateral hemisphere, for example, in patients with tuberous sclerosis complex. We did not intend to remove all cortical sites showing mild glucose hypometabolism with 10% relative hypometabolism compared with the homotopic region, since our previous study showed that failure to remove the areas with such mild glucose hypometabolism was not associated with poor surgical outcome (Juhász *et al.*, 2001). To confirm that the intended surgical procedure was indeed achieved, intraoperative photographs were obtained with a digital camera immediately following cortical resection and post-operative MRI was obtained 1–3 days after the cortical resection.

Measurement of surgical outcome

Surgical outcomes were prospectively obtained using regular postoperative follow-up assessments or using phone-call interviews for patients from out of state. Surgical outcome was classified in four grades according to Engel's classification (Engel *et al.*, 1993; Valentin *et al.*, 2005). In short, Class I outcome represents: 'free of disabling seizures for at least two years'. Class I outcome consists of the following four subcategories. Class IA outcome represents: 'completely free of any type of seizures since surgery'. Class IB outcome represents: 'free of disabling seizures since surgery but non-disabling simple partial seizures noted'. Class IC outcome represents: 'some disabling seizures noted early after surgery but free of disabling seizures for at least two years'. Class ID outcome represents: 'free of disabling seizures but generalized convulsion noted only following antiepileptic drug withdrawal'. Class II outcome represents: 'rare disabling seizures (three or less disabling seizures per year)'. Class III outcome represents: 'worthwhile improvement (at least 90% reduction in seizure frequency)'. Class IV outcome represents: 'no significant improvement (<90% reduction in seizure frequency)'. Class I outcome was treated as success in the present study, whereas Class II, III and IV outcomes were treated as failure. This analytic approach was judged appropriate because of the following reasons. First, a number of previous studies have attempted to determine predictors of Class I outcome following surgery (Chang *et al.*, 2008; Elsharkawy *et al.*, 2008). Second, application of a common outcome measure may facilitate collaboration and comparison across centers, as suggested by the Commission on Neurosurgery of the International League Against Epilepsy (Cross *et al.*, 2006). Third, it has been reported that Class IA outcome is difficult to achieve in many patients with neocortical epilepsy in whom invasive presurgical evaluation using subdural grid electrodes was required (Pondal-Sordo *et al.*, 2006; Widdess-Walsh *et al.*, 2007; Jayakar *et al.*, 2008).

Statistical analysis

Using univariate and multiple logistic regression models, we determined whether the long-term surgical outcome was predicted by patient demographic profiles, seizure frequency, ECoG variables and neuroimaging variables. The outcome measure of interest ($Y_{\text{Class I}}$) was 'achievement of Engel's Class I outcome following the initial cortical resection'; ($Y_{\text{Class I}}$) was given a score of 1 if a patient obtained Class I outcome, and 0 otherwise. Class I outcome following a second surgery (i.e. re-operation) was considered as a failed surgery in the present study. The predictor variables in the present study included: (i) age (X_{Age}); (ii) seizure frequency (X_{Daily}); (iii) history of epileptic spasms (X_{Spasm}); (iv) presence or absence of cortical tumour on MRI (X_{Tumour}); (v) presence or absence of any cortical lesions on MRI (X_{Lesion}); (vi) completeness of removal of 'cortical abnormalities on neuroimaging' (X_{Image}); (vii) whether or not seizures were captured during ECoG recording (X_{Sz}); (viii) completeness of removal of seizure

onset zone (X_{Onset}); (ix) the frequency of interictal spikes at the site showing the maximal spike frequency among the whole subdural electrode arrays (X_{Maxsp}) and (x) the frequency of interictal spikes at the site showing the maximal spike frequency among the surgically-preserved sites (X_{Remsp}). For selection of the predictor variables described above, the total number of patients studied in the present study and collinearity problems among the predictor variables (Cohen *et al.*, 2002) were taken into account. The limitations of regression analyses in the present study are described in the discussion below.

The univariate linear regression model tested here is shown below:

$$\text{logit} [\text{Probability of } Y_{\text{Class I}} = 1] = \beta_0 + \beta_i \cdot X_i$$

($i = \text{Age, Daily, Spasm, Tumour, Lesion, Image, Sz, Onset, Maxsp and Remsp}$).

The full multiple logistic regression model tested here is shown below.

$$\begin{aligned} \text{logit} [\text{Probability of } Y_{\text{Class I}} = 1] = & \beta_0 + \beta_{\text{Age}} \cdot X_{\text{Age}} + \beta_{\text{Daily}} \cdot X_{\text{Daily}} \\ & + \beta_{\text{Spasm}} \cdot X_{\text{Spasm}} + \beta_{\text{Tumour}} \cdot X_{\text{Tumour}} \\ & + \beta_{\text{Lesion}} \cdot X_{\text{Lesion}} + \beta_{\text{Image}} \cdot X_{\text{Image}} + \beta_{\text{Sz}} \cdot X_{\text{Sz}} \\ & + \beta_{\text{Onset}} \cdot X_{\text{Onset}} + \beta_{\text{Maxsp}} \cdot X_{\text{Maxsp}} + \beta_{\text{Remsp}} \cdot X_{\text{Remsp}} \end{aligned}$$

In these models, (X_{Age}) was given a score according to the age of patient at surgery [years]; (X_{Daily}) was given a score of 1 if a patient had daily disabling seizures during a three-month period prior to surgery and 0 otherwise; (X_{Spasm}) was given a score of 1 if a patient had a history of epileptic spasms and 0 otherwise; (X_{Tumour}) was given a score of 1 if a patient had a cortical tumour visible on MRI and 0 otherwise; (X_{Lesion}) was given a score of 1 if a patient had a cortical lesion visible on MRI and 0 otherwise; (X_{Image}) was given a score of 1 if cortical abnormalities on neuroimaging failed to be completely removed and 0 otherwise; (X_{Sz}) was given a score of 1 if a patient had at least one seizure captured during extraoperative ECoG recording and 0 otherwise; (X_{Onset}) was given a score of 1 if the seizure onset zone failed to be completely removed and 0 otherwise; (X_{Maxsp}) was given a score according to the frequency of interictal spikes (unit: min^{-1}) at the site showing the maximal spike frequency among the whole subdural electrode arrays; (X_{Remsp}) was given a score according to the frequency of interictal spikes (unit: min^{-1}) at the site showing the maximal spike frequency among the surgically preserved sites.

In addition to the full multiple logistic regression model described above, we tested how well the surgical outcome was predicted by a reduced logistic regression model not incorporating interictal ECoG measures [(X_{Maxsp}) and (X_{Remsp})] and another reduced logistic regression model not incorporating ictal ECoG measures [(X_{Sz}) and (X_{Onset})]. Each regression model yielded an ' R^2 value', which is an indicator of fitness of the logistic regression model. On the other hand, each of the three multiple logistic regression models yielded the probability of obtaining Class-I outcome in each subject; a receiver operating characteristic (ROC) curve was then derived by plotting true-positive rates against false-positive rates, while the threshold for prediction of outcome varied from 0 to 1 (Hanley and McNeil, 1983). Each of the three multiple logistic regression models finally yielded 'the area under the ROC curve', which is a measure of the overall discriminatory power of each predictive regression model. An area under the ROC curve of 0.5 indicates random prediction, whereas a value of 1.0 indicates perfect discrimination. Using ' R^2 value' and 'the area under the ROC curve' derived from each of the three multiple logistic regression models, we estimated how outcome-prediction could be improved by adding spike frequency measures to the other conventionally available diagnostic

measures such as ictal ECoG and neuroimaging data. Similarly, we estimated how lack of ictal ECoG measures affected the ability of outcome–prediction using the logistic regression approach.

All statistical analyses were performed using the computer software SPSS 11.5 (SPSS Inc, Chicago, IL, USA). A significance level of 0.05 was used.

Results

Surgical outcome

Following the initial cortical resection, Engel Class I, II, III and IV were noted in 35, 6, 12 and 7 patients, respectively. Engel Class IA, IB, IC and ID were noted in 26, 4, 4 and 1 patients, respectively. None of the patients underwent multiple subpial transections. One child died due to disseminated intravascular coagulation associated with pseudomonas sepsis derived from a urinary tract infection 2 days after surgery. Subsequently, the parents disclosed that they had been supplementing this child with a cocktail of immune-enhancing medications that they had obtained from overseas. Thus, the logistic regression analyses were applied to the remaining 60 subjects whose long-term seizure outcomes were available [follow-up period: 2.5–6.4 years (mean 4.6 years); Supplementary Table 1].

Five patients who initially failed to obtain Class I outcome underwent a second epilepsy surgery. Two patients with Class IV outcome resulted in Class I outcome following the second surgery; another patient with Class IV outcome resulted in Class III outcome following the second surgery. Two patients with Class III outcome resulted in Class II outcome following the second surgery. In the present study, Class I outcome following the second surgery was treated as a failed surgery, and the surgical outcome following the initial cortical resection was used as the outcome measure of interest in the logistic regression analyses.

Univariate logistic regression analyses

The detailed results of univariate logistic regression analyses are described in Table 1. The univariate logistic regression analyses demonstrated that (i) the chance to obtain Class I outcome was lower in patients whose seizure onset zones were incompletely removed compared with the others ($P=0.003$); (ii) the chance to obtain Class I outcome was lower in patients whose cortical abnormalities on neuroimaging were incompletely removed compared with the others ($P=0.05$); (iii) smaller frequency of interictal spikes at the preserved site was associated with the greater chance to obtain Class I outcome ($P=0.03$).

Full multivariate logistic regression analysis to determine the independent predictor of surgical outcome

The detailed results of multivariate logistic regression analyses are described in Table 2 and Fig. 1. The full multivariate logistic regression model demonstrated that the chance to obtain Class I outcome was lower in patients whose seizure onset zones were incompletely removed compared with the others and that incomplete removal of seizure onset zone was the only independent predictor of failure to obtain Class I outcome ($P=0.01$).

Comparison between full and reduced multivariate logistic regression models

The goodness of regression model fit and the predictive ability of regression model were greatest in the full regression model incorporating both ictal and interictal measures (R^2 0.44; area under the ROC curve: 0.81), slightly smaller in the reduced model incorporating ictal but not interictal measures (R^2 0.40; area under the ROC curve: 0.79) and slightly smaller still in the reduced model incorporating interictal but not ictal measures (R^2 0.27; area under

Table 1 Odds ratios in the univariate logistic regression analysis

	Odds ratio	P-value	Rate of Class I outcome	Rate of Class I outcome
Age	1.03	0.6		
Seizure frequency	0.42	0.1	Daily seizures: 18/36	<Daily seizures: 17/24
Epileptic spasms	0.71	0.5	Yes: 10/19	No: 25/41
Cortical tumor on MRI	2.88	0.2	Yes: 7/9	No: 28/51
Cortical lesion on MRI	1.90	0.3	Yes: 27/43	No: 8/17
Completeness of removal of neuroimaging abnormalities	0.31	0.05	Complete: 29/44	Incomplete: 6/16
Availability of ictal ECoG data	1.43	0.7	Yes: 33/56	No: 2/4
Completeness of removal of seizure onset zones	0.04	0.003	Complete: 34/48	Incomplete: 1/12
Maximal spike frequency across the whole electrodes	0.99	0.6		
Maximal spike frequency among the preserved sites	0.89	0.03		

An odds ratio (and P -value) for each predictor variable is described. Class I outcome was noted in 18 of the 36 patients with daily seizures and in 17 of the 24 patients with less than daily seizures. Class I outcome was noted in 10 of the 19 patients with a history of epileptic spasms and in 25 of the 41 patients without. Class I outcome was noted in seven of the nine patients with a cortical tumour seen on MRI and in 28 of the 51 patients without. Class I outcome was noted in 27 of the 43 patients with a cortical lesion seen on MRI and in eight of the 17 patients without. Class I outcome was noted in six of the 16 patients whose cortical abnormalities on neuroimaging failed to be completely removed and in 29 of the other 44 patients. Class I outcome was noted in 33 of the 56 patients who had at least one seizure captured during extraoperative ECoG recording and in two of the four patients who failed to develop a seizure during ECoG recording. Class I outcome was noted in only one of the 12 patients whose seizure onset zones failed to be completely removed and in 34 of the other 48 patients'.

Table 2 Odds ratios in three multivariate logistic regression models

	Multivariate full model	Multivariate reduced model without interictal ECoG measures	Multivariate reduced model without ictal ECoG measures
Age	1.01; $P=0.9$	1.01; $P=0.9$	0.96; $P=0.6$
Seizure frequency	0.44; $P=0.4$	0.38; $P=0.3$	0.41; $P=0.4$
Epileptic spasms	2.34; $P=0.4$	1.32; $P=0.7$	2.08; $P=0.4$
Cortical tumor on MRI	0.62; $P=0.7$	0.60; $P=0.6$	1.26; $P=0.8$
Cortical lesion on MRI	1.84; $P=0.5$	2.50; $P=0.3$	1.95; $P=0.4$
Completeness of removal of neuroimaging abnormalities	0.42; $P=0.3$	0.33; $P=0.2$	0.23; $P=0.06$
Availability of ictal ECoG data	6.30; $P=0.2$	5.15; $P=0.2$	(Not incorporated)
Completeness of removal of seizure onset zones	0.05; $P=0.01$	0.05; $P=0.009$	(Not incorporated)
Maximal spike frequency across the whole electrodes	1.00; $P=0.9$	(Not incorporated)	1.01; $P=0.6$
Maximal spike frequency among the preserved sites	0.90; $P=0.2$	(Not incorporated)	0.89; $P=0.1$
Constant	0.62; $P=0.8$	0.59; $P=0.7$	3.55; $P=0.4$

An odds ratio (and P -value) for each predictor variable is described. The full logistic regression model as well as reduced model taking into account ictal ECoG measures demonstrated that the chance to obtain a Class I outcome was significantly lower in patients whose seizure onset zones were incompletely removed compared with those whose seizure onset zones were completely removed.

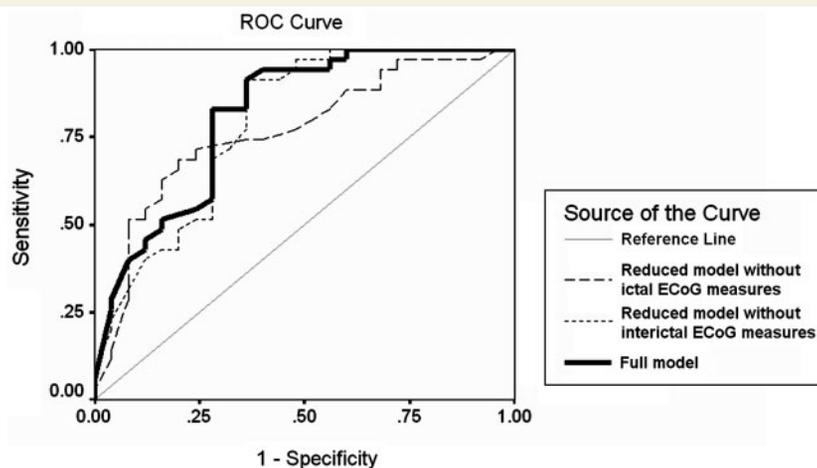


Figure 1 ROC curves for three logistic regression models. The area under the ROC curve was 0.81 in the full regression model incorporating both ictal and interictal measures, 0.79 in the reduced model incorporating ictal but not interictal measures and 0.77 in the reduced model incorporating interictal but not ictal measures. All of these areas under the ROC curve were significantly greater than 0.5 ($P < 0.001$).

the ROC curve: 0.77). ROC curves for these models are described in Fig. 1.

Discussion

The major findings in the present study can be summarized in four points: (i) The univariate logistic regression analyses suggested that incomplete removal of seizure onset zone, higher interictal spike-frequency in the preserved cortex and incomplete removal of cortical abnormalities on neuroimaging were associated with a greater risk of failing to obtain Class I outcome; (ii) the full multivariate logistic regression model suggested that incomplete removal of seizure onset zone was the only independent predictor of failure to obtain Class I outcome; (iii) comparison of the goodness of

regression model fit and the predictive ability of regression model between the full and reduced regression models indicated that the additive clinical impact of interictal spike frequency measures to predict the long-term surgical outcome may be modest in the presence of ictal ECoG and neuroimaging data; and (iv) exclusion of ictal ECoG measures from the full regression model resulted in a worse regression model fit (R^2 0.44 \rightarrow 0.27).

Significance of seizure onset zones in epilepsy surgery

The observation that incomplete removal of seizure onset zone was a significant predictor of failure to obtain Class I outcome is consistent with the generally accepted notion that the seizure

onset zone frequently consists of a part of the overall epileptogenic zone (Lüders *et al.*, 1993). Previous studies of a large series of children and adults with focal epilepsy demonstrated that incomplete resection of seizure onset zones on extraoperative ECoG recording was a risk factor of poor surgical outcomes (Jeha *et al.*, 2007; Widdess-Walsh *et al.*, 2007; Jayakar *et al.*, 2008). The risk of seizure recurrence associated with incomplete resection of seizure onset zones should be considered prior to the surgical procedure, although seizure onset zones on ECoG recording are not the perfect gold standard for localizing the epileptogenic zone due to an unavoidable risk of sampling errors.

As described in both previous studies (Jeha *et al.*, 2007; Widdess-Walsh *et al.*, 2007; Jayakar *et al.*, 2008) and the present study, the extent of cortical resection was often limited by the location of eloquent cortices. Should we have performed multiple subpial transections on such areas? It still remains unknown whether multiple subpial transections of the seizure onset zone involving the eloquent cortices could have improved the long-term seizure outcome. A previous study using meta-analysis of 76 studies suggested that only 16% of the patients who needed multiple subpial transections on the eloquent cortices obtained a long-term seizure-free outcome (Télez-Zenteno *et al.*, 2005).

Significance of interictal spike frequency measures in epilepsy surgery

The novel approach in the present study includes quantitative measurement of interictal spike frequency at each subdural electrode site. The univariate logistic regression analysis demonstrated that higher interictal spike-frequency in the preserved cortex was associated with a greater risk of failing to obtain Class I outcome. An increase in interictal spike frequency by 1 spike/min was associated with a reduction in odds of obtaining Class I outcome by 0.89. This observation is consistent with the generally accepted notion that interictal spike activities are a biomarker for the underlying pathophysiology of the epileptic condition (Krendl *et al.*, 2008; Miller and Gotman, 2008). The cortical sites generating interictal spikes have been also known as the irritative zone and interictal spikes are considered as mini-seizures, since spikes can give rise to clinical symptoms when they are of sufficient strength and are generated within an eloquent cortical area (Rosenow and Lüders, 2001). Thus, the risk of seizure recurrence associated with incomplete resection of irritative zone should be considered prior to the surgical procedure, especially when ictal events are not captured during ECoG recording but frequent interictal spikes are observed.

Then, how was outcome-prediction improved by adding spike frequency measures to the other conventionally available diagnostic measures such as ictal ECoG and neuroimaging data? The present study suggests that the additive impact of interictal spike frequency measures was modest, if any, in the presence of ictal ECoG and neuroimaging data. The full multivariate logistic regression analysis demonstrated that none of the interictal ECoG measures but incomplete removal of seizure onset zone was the

only independent predictor of failure to obtain Class I outcome. Furthermore, adding spike frequency measures to the multivariate logistic regression model only modestly increased the goodness of regression model fit and the predictive ability of regression model (R^2 0.40 \rightarrow 0.44; area under the ROC curve: 0.79 \rightarrow 0.81).

It still remains unknown whether we could have obtained the equivalent surgical outcome without using ictal ECoG data, since the present study was not designed to directly answer such a question. The present study showed that exclusion of ictal ECoG measures from the full regression model resulted in a worse regression model fit (R^2 0.44 \rightarrow 0.27); here, an R^2 of 0.44 indicates that 44% of the outcome measures can be explained by the full regression model. Thus, the present study failed to provide strong evidence suggesting that the equivalent surgical outcome could have been obtained without using ictal ECoG data.

Significance of cortical abnormalities on neuroimaging in epilepsy surgery

The present study suggested that complete resection of cortical abnormalities on neuroimaging is an important factor to obtain a good long-term surgical outcome. The univariate logistic regression analysis revealed that incomplete removal of cortical abnormalities on neuroimaging was associated with a greater risk of failing to obtain Class I outcome. This result is consistent with the observations in previous studies of a large series of children and adults with focal epilepsy (Janszky *et al.*, 2000; Chang *et al.*, 2008; Cossu *et al.*, 2008; Fauser *et al.*, 2008). A previous study of 332 patients with low-grade gliomas (Chang *et al.*, 2008) and a study of 120 patients with histologically proven focal cortical dysplasias (Fauser *et al.*, 2008) reported that complete resection of MRI-visible lesions was associated with a better seizure outcome compared with incomplete resection. A previous PET study of 26 patients with non-lesional temporal lobe epilepsy showed that complete resection of cortical areas showing significant glucose hypometabolism defined by a statistical parametric mapping approach ($P < 0.0005$ and pixel cluster > 200) was associated with a better seizure outcome compared with incomplete resection (Vinton *et al.*, 2007).

Our present findings are not inconsistent with a previous study from our group that showed no correlation between extent of non-resected cortical hypometabolism and surgical outcome in neocortical epilepsy (Juhász *et al.*, 2001); in that study, unlike in the present report, cortical areas with even mild (10–15% decrease, as compared with the contralateral homotopic region) hypometabolism were included. It is likely that a significant proportion of mild cortical hypometabolism represents non-epileptic cortex and FDG PET generally overestimates epileptogenic cortex to be resected (Juhász *et al.*, 2000). Further prospective studies are warranted to determine how well other advanced imaging modalities, such as [^{11}C]flumazenil PET (Juhász *et al.*, 2001, 2009) or magnetic source imaging (Knowlton *et al.*, 2008; Sutherling *et al.*, 2008) can eventually improve prediction of the long-term surgical outcome.

Limitations in the present study

Limitations of the present study must be considered. Interictal ECoG measures of interest were limited to 'frequency' alone in the present study. Neither 'amplitude' nor 'latency' between spikes in different sites was taken into analysis. Since the present study is a prospective study, we wanted to collect all predictor measures by the end of cortical resection. We recognized that measurement and human validation of all of 'frequency', 'amplitude' and 'latency' of interictal spikes were not tenable, due to the limited time frame between the placement of subdural electrodes and subsequent cortical resection. Limitations of the present study also include a limited sampling rate of 200 Hz during ECoG data collection. According to the Nyquist–Shannon sampling theorem, our data acquisition system could only study oscillations slower than 100 Hz. Previous studies of patients with focal epilepsy using intracranial monitoring demonstrated that the seizure-onset area was often associated with interictal high-frequency oscillations at 80–500 Hz (Bragin *et al.*, 2002; Clemens *et al.*, 2007; Jacobs *et al.*, 2008). Further studies are warranted to determine whether outcome prediction can be improved by measuring the 'amplitude' and 'latency of interictal spikes or interictal high-frequency oscillations.

The 'extent' of areas showing frequent interictal spikes was indirectly taken into account in the present study. We presumed that patients who had extensive areas showing frequent interictal spikes had a larger risk of some spiking areas remaining following focal cortical resection, compared to those with restricted areas showing frequent interictal spikes.

In the present study, intraoperative ECoG measures immediately following cortical resection were not incorporated into the multivariate logistic regression analysis. It still remains unknown how well postoperative ECoG can improve prediction of the long-term surgical outcome. Some studies of patients with focal epilepsy using postoperative ECoG recording showed that frequent spikes as well as ictal discharges in the preserved areas were associated with poor surgical outcome (Wennberg *et al.*, 1998; MacDonald and Pillay, 2000; McKhann *et al.*, 2000; Ferrier *et al.*, 2001; Pondal-Sordo *et al.*, 2006). Other studies showed that interictal spikes on intraoperative ECoG recording immediately following cortical resection were not predictive of surgical outcome (Cascino *et al.*, 1995; Kanazawa *et al.*, 1996; Schwartz *et al.*, 1997; Gröppel *et al.*, 2003). We have also reported that general anaesthesia often reduces the absolute spike frequency in patients with focal epilepsy (Asano *et al.*, 2004). On the other hand, it was also reported that some patients with focal epilepsy associated with brain tumour may develop new post-resection spikes following lesionectomy despite normal pre-resection ECoG and that such reactive post-resection spikes were not predictive of clinical seizures (Schwartz *et al.*, 2000).

For selection of the predictor variables, collinearity problems among the predictor variables (Cohen *et al.*, 2002) were taken into account in the present study. For example, the frequency of seizures but not the duration of epilepsy was incorporated into the multivariate logistic regression analyses. A previous study of

171 adults with temporal lobe epilepsy associated with hippocampal sclerosis showed that longer duration of epilepsy was associated with poor long-term seizure outcome (Janszky *et al.*, 2005). We recognized that the duration of epilepsy could be affected by collinearity problems with the age of patient and that assumption of linear relationship between duration and severity of epilepsy may not be tenable in the present study of children with various forms of underlying etiologies. In addition, the duration of epilepsy could be difficult to determine when the first seizure occurred during infancy and medically uncontrolled focal seizures occurred at adolescence following a long-term remission. Although some patients underwent either or both [¹¹C]flumazenil PET and/or α-[¹¹C]methyl-L-tryptophan PET in our institute, these diagnostic modalities were not incorporated into the multiple logistic regression analyses, because of potential collinearity problems. [¹¹C]flumazenil PET has been often applied to patients who failed to reveal a lesion on MRI (Juhász *et al.*, 2001, 2008), whereas α-[¹¹C]methyl-L-tryptophan PET has been often applied to patients with brain tumour (Juhász *et al.*, 2006) and those with multiple cortical tubers across both hemispheres (Kagawa *et al.*, 2005). Instead of incorporating these PET modalities, we incorporated the presence of cortical lesions on MRI, the presence of cortical tumour on MRI and incomplete resection of cortical abnormalities on neuroimaging into the multiple logistic regression analyses in the present study.

Supplementary material

Supplementary material is available at *Brain* online.

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