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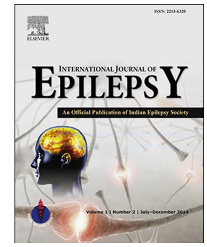

Original Article

Utility of invasive ictal EEG recordings in pre-surgical evaluation of patients with medically refractory temporal lobe epilepsy and normal MRI

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ABSTRACT

Purpose: Some previous studies have suggested that invasive ictal recording may be omitted in patients with medically refractory temporal lobe epilepsy (TLE) that have localizing scalp ictal recordings despite having normal magnetic resonance imaging (MRI). We investigated if and how often invasive ictal recording provided additional information to their pre-surgical evaluations.

Methods: In a retrospective review of 302 patients with intractable TLE who underwent pre-surgical evaluation between 1991 and 2006, we identified 45 patients who had normal MRI. Localization by scalp ictal recording, invasive ictal recording, and surgical procedures were obtained from medical records. Primary outcome was measured by comparing the concordance of localization by scalp and invasive ictal recordings and surgery to determine if invasive ictal recording provided additional information.

Results: Twenty-five patients were included in the analysis. Invasive ictal recordings were concordant in 72.0% (18/25) of the patients with unilateral temporal onset found on scalp ictal recording. 28.0% (7/25) of patients had their surgical plan altered by the results of invasive ictal recording. 61.1% (11/18) of patients who received anterior temporal lobectomies (ATL) remained seizure-free. Of the patients who received different surgeries based on invasive ictal recording, 80.0% (4/5) remained seizure-free.

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Conclusions: Our study showed that findings from invasive ictal recording changed the type of surgery in 28.0% of the patients. Invasive ictal recording may not be an absolute prerequisite for resective epilepsy surgery in some patients with intractable TLE with a supposedly normal MRI of the brain but may alter the surgical decision.

1. Introduction

Two million people have been diagnosed with epilepsy in the United States,[1] of which, more than 20% are medically refractory.[2] Temporal lobe epilepsy (TLE), with a specific pathophysiology of hippocampal sclerosis (HS), is the most common form of focal epilepsy and is most medically refractory.[3,4] In patients with newly diagnosed epilepsy, failure to control their seizures after trials of two anti-epileptic medications indicates a less than 5% chance in rendering them seizure-free with a third or fourth agent.[5] Patients with medically refractory TLE and HS may be candidates for anterior temporal lobectomy (ATL), which has been reported to be 50-85% successful in rendering the patients seizure-free.[6–9] Ictal scalp EEG recordings have long been used to localize the epileptogenic zone for surgical resections.[10,11] History of febrile seizures, the presence of signal/volume change on magnetic resonance imaging (MRI), and interictal/ictal EEG/MRI concordance have been shown to be predictors for good surgical outcome, i.e., post-operative seizure-freedom.[12,13] Investigators have further demonstrated that interictal epileptiform discharges (IEDs) on scalp EEG, when concordant with MRI and/or FDG-PET abnormalities, correspond to good surgical outcome in patients who subsequently undergo ATL for treatment of their medically refractory TLE.[14–17] Various neuro-imaging modalities are used to identify specific structural and physiologic abnormalities in patients undergoing pre-surgical evaluations.[18] MRI has become an integral part of pre-surgical evaluation in these patients.[19–22] In a study of 222 patients with medically refractory TLE, Scott et al. found that 18% of them had no signal or volume abnormality on MRI.[23] Other investigators have shown that the surgical outcomes in these patients have improved over the past 15 years, from 16-27% seizure-free to 41-60%.[24–28] Some of the studies have gone further to suggest that invasive ictal recording may be omitted in some of these patients, in the setting of limited resources (though careful attention to subtle MRI findings and poorer surgical outcomes were emphasized).[28,29] Therefore, we sought to estimate the additional yield of invasive recordings to the pre-surgical evaluations in patients with medically refractory TLE and normal MRI.

2. Methods

This study was approved by the institutional review board at the University of Florida. Adult patients were identified from the University of Florida Comprehensive Epilepsy Program epilepsy surgery database as to if they underwent pre-surgical evaluation for medically refractory TLE between 1991 and 2006, had normal pre-operative MRI by report, and at least 6 months of post-operative follow-up. Historical clinical data, results from video-EEG monitoring, MRI, and histopathology were obtained from medical records.

All MRI studies were performed on 1.5T magnetic resonance scanners (GE Signa or Siemens Sonata). Preoperative MRI sequence protocol included: spin echo T1 in sagittal plane, fast T2-w FLAIR in axial and coronal planes, fast spin echo T2-w sequence with the gantry angled to be orthogonal to the long axis of the hippocampus, axial DWI (diffusion weighted) sequence, and axial 3D MP Rage (T1-w) obtained in axial plane but capable of reconstruction in any plane. The slice thickness and interleave gap were 4 mm/1 mm for all but the gradient T1-w sequence, which was 1.5 mm thickness. Patients were excluded because of reported MRI lesions, such as neoplasm, cortical dysplasia, HS, or vascular malformations. Patients with subtle or questionable MRI findings, at the time of the decision to proceed with resective epilepsy surgery, were also excluded.

All scalp EEG were recorded with the international 10–20 system with added mandibular electrodes (MN1/2). EEG data was acquired on Nicolet BMSI 6000, Viasys, and XLTek systems, sampling at 256 Hz. Invasive EEG was recorded on Nicolet BMSI 6000 and Viasys systems at a sampling rate of 256 Hz, with either implanted subdural grid electrodes or bilateral depth electrodes (through an occipital approach), with concurrent scalp EEG recordings. The ictal EEG data were obtained during the in-patient video-EEG monitoring study, continuously in sleep and wake cycles and during routine activation procedures, i.e. hyperventilation and photic stimulation. The interictal EEG data were obtained during the in-patient video-EEG monitoring study, as well as routine outpatient EEG. All EEG reports were reviewed without prior knowledge of the patients' post-operative outcome to obtain information on electrographic localization of seizure onset and IEDs.

The diagnosis of TLE and the localization of seizure onset were obtained from medical records. Localization by scalp ictal recording was divided into left-temporal, right-temporal, bi-temporal, and extra-temporal. Localization by invasive ictal recording was classified as left/right mesial/lateral temporal, bi-temporal, extra-temporal, and multifocal. Surgery was categorized as left/right ATL, extra-temporal resection, and no surgery. Surgical outcome was assessed and classified according to Engel classifications of seizure-freedom.[30] Our primary analysis compared surgical outcomes to the concordance of localization by scalp and invasive ictal recordings to determine if invasive ictal recording provided additional information.

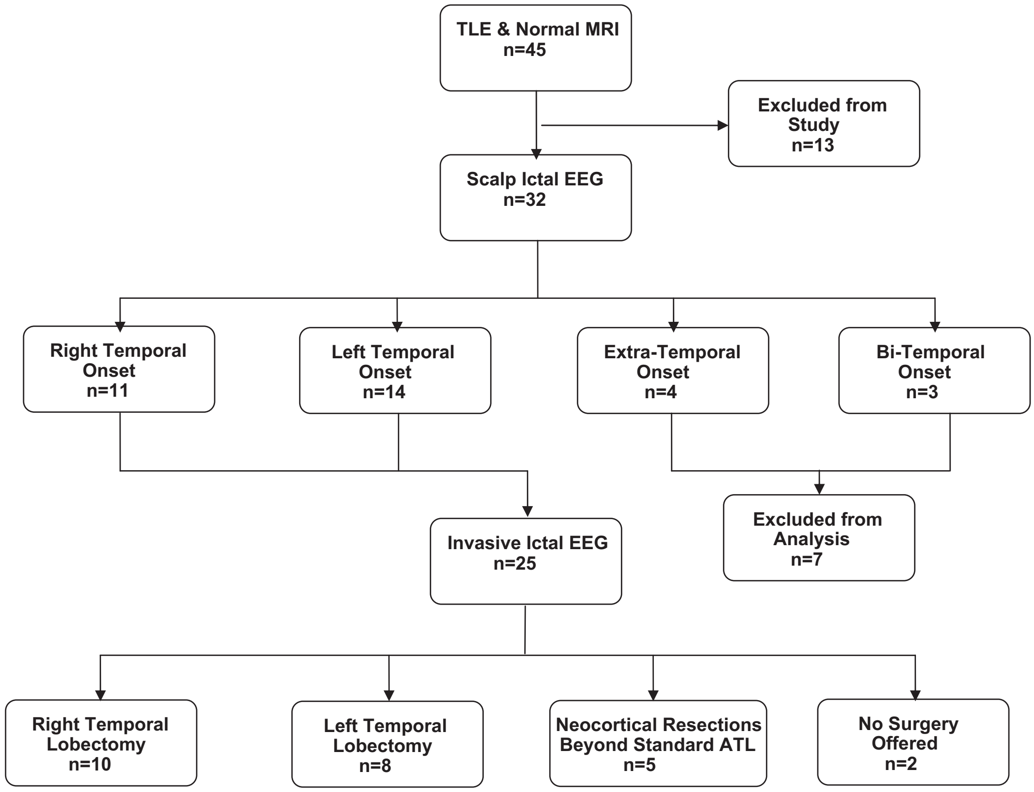

Fig. 1 – Overview of patient evaluations and surgery decisions in 45 patients with TLE and normal MRI.

3. Results

3.1. *Patient demographics*

In this retrospective review of 302 patients with intractable TLE who underwent pre-surgical evaluation, we identified 45 patients who had normal MRI. Eleven of the 45 patients were excluded due to incomplete medical records, and two other patients were excluded due to other medical issues during the course of their pre-surgical evaluation. The patients were followed up post-operatively between 6 and 135 months, with the median follow-up period of 20.5 months. Their ages ranged from 19 to 58. All patients had tried at least three anti-epileptic medications and continued to experience seizures, at least monthly seizures, prior to surgery.

3.2. *EEG*

See Fig. 1 for overview of patient evaluations and surgery. Of the 32 patients in the study, scalp ictal EEG identified four patients as extra-temporal onset and three patients as bi-temporal independent onset, and they were excluded from the analysis. Of the remaining 25 patients, 11 patients were identified by scalp ictal EEG as right-temporal lobe onset and 14 patients were identified as left-temporal lobe onset. Ten of the 11 patients identified as right-temporal lobe onset were found to have concordant in scalp and invasive ictal recordings whereas eight of 14 patients identified as left-temporal lobe onset on scalp ictal recordings were concordant in their invasive ictal recordings. Therefore, invasive ictal recordings were concordant in 72.0% (18/25) of the patients with unilateral-temporal onset found on scalp ictal recordings, and these patients underwent ATL on the respective sides. Seven of the 25 patients (28.0%) had their surgical plan altered by the results of invasive ictal recording. Five patients underwent surgical resections other than ATL, e.g., neocortical resections beyond the standard ATL. One patient was not offered surgery due to the findings of multifocal seizure onset areas in the invasive ictal recordings. The other patient was not offered surgery as his epileptogenic zone was found to be extra-temporal and was functionally mapped to eloquent cortex.

3.3. *Histopathology*

Refer to Table 1 for histopathology and surgical outcomes in 23 patients who underwent surgical resection. HS was seen in

Table 1 – Histopathology vs. outcome in 23 patients with TLE and normal MRI who underwent surgical resection directed by invasive ictal recordings.

	Engel Ia & Ib	Engel II	Engel III
Hippocampal sclerosis	2	1	0
Heterotropia	2	0	0
Arteriovenous malformation	1	0	0
Non-specific gliosis	0	0	2
Normal	12	3	0

only three of the 23 specimens, heterotropia in two, and vascular malformation was seen in one specimen. Of the remaining 17 specimens, 2 demonstrated non-specific gliosis and 15 were normal tissues.

3.4. *Surgical outcome*

Table 1 shows the post-operative seizure-freedom of each patient as a function of histopathology. The patients were followed post-operatively between 6 and 135 months, with the median follow-up period of 20.5 months. Of the patients who received ATL, 61.1% were found to remain seizure-free (Engel Classifications Ia & Ib). For those who received resections other than ATL, 80.0% remained seizure-free (Engel Classifications Ia & Ib).

4. Discussion

Our results validate previous reports that invasive ictal EEG recordings have an important role in the pre-surgical evaluation in patients with medically refractory TLE and normal MRI of the Brain.[31–36] In our study, findings from the invasive ictal recordings demonstrated a 28.0% discordance with the scalp ictal recordings in patients with medically intractable TLE and normal MRI. This discordance either modified the type of surgery actually performed or resulted in the decision to not offer resective epilepsy surgery. Invasive ictal EEG recordings revealed different epileptogenic zones in their ictal scalp EEG in seven of 25 patients (1/11 right-temporal onset and 6/14 left-temporal onset). Of these seven patients, five received neocortical resections beyond standard ATL with 80% (4/5) of them becoming seizure-free. More importantly, the invasive ictal EEG recording of one patient showed multi-focal ictal onset, and in the other patient, the invasive ictal EEG recording demonstrated an extra-temporal ictal onset that was functionally mapped to an eloquent cortex. Thus, these two patients were not offered surgery because of the findings of their invasive ictal EEG recordings. We could not assess whether a standard ATL in the 5 patients who had a tailored resection based on invasive recordings would have also resulted in a seizure-free outcome. This should be weighted against the added risk of morbidity and mortality associated with invasive recordings. Our study has numerous limitations. First and foremost, this is a retrospective study with inherent limitations. The number of patients with truly negative MRI findings has been decreasing with the advent of higher resolution MRI studies that were not available with the earlier patients in this study. However, despite the advancement in MRI technology, 40–48% patients with intractable TLE undergoing pre-surgical evaluation were found to have negative high-resolution MRI,[37,38] which is a larger fraction of normal MRI than in our patients. Bell et al. who advocated not precluding patients with MRI negative TLE as candidates for resective epilepsy surgery stressed the importance of evaluating MRI of the brain for subtle abnormalities.[29] As the surgical decisions were based on the interpretations of the MRI and EEG recordings at that time, we decided not to reinterpret the studies in our series. Newer non-invasive investigations, such as Magnetoencephalography (MEG) and Subtraction Ictal Single-Photon Emission Computed Tomography (SPECT) Co-registered to MRI (SISCOM), that were not done in our series may, in settings where they are available and performed, reduce the population of patients who needs invasive ictal recording.

Holmes and colleagues examined 23 patients with medically refractory TLE and normal MRI who underwent ATL and found that 48% of them remained seizure-free (Engel Classifications Ia & Ib).[26] In those patients, all had ictal surface EEG recordings and six also underwent placement of subdural strip electrodes bilaterally over the lateral and mesial temporal surfaces for invasive ictal EEG recordings. However, it is unclear how many of the patients who had only ictal surface EEG recordings prior to their ATL were among the 11 who were seizure-free at follow-up. In the study by Bell et al. of 40 patients with medically refractory TLE and normal MRI who underwent ATL, 60% (24/40) were seizure-free.[29] Only nine patients underwent invasive EEG monitoring, in whom only 33% (3/9) became seizure-free post-operatively. Although the remaining 31 patients had only ictal surface EEG recordings, 93% (37/40) of all the patients underwent intra-operative recordings via subdural strip electrodes over the superior and inferior temporal gyri, and depth electrodes orthogonally through the middle temporal gyrus into the amygdala and hippocampus in order to guide the resections. These studies demonstrated that a subgroup of patients with medically refractory TLE and normal MRI can achieve good surgical outcome. However, these studies examined the surgical outcome in patients who had already undergone ATL, with and without preceding invasive ictal EEG recordings.[26,29] Therefore, these studies could not demonstrate whether invasive ictal EEG provided additional information and thus cannot be used to determine if it can be obviated from the pre-surgical evaluation in patients with medically refractory TLE and normal MRI. In contrast, the primary outcome in our study was measured by comparing the concordance of localization by scalp and invasive ictal recordings and the type of surgery to determine the additional information invasive ictal recordings provided.

In our study, the post-operative seizure-freedom rate for patients who underwent AMTL was 61.1%, comparable to that in other studies. An additional 27.8% of them had significant reduction in seizure frequency (Engel Classification II). In the patients who received neocortical resections in addition to ATL because of findings on their invasive ictal EEG recordings, the post-operative seizure-freedom rate was 80.0%. However, the higher percentage may be accounted for by the low number of patients in this subgroup (4/5). The one patient who did not become seizure-free had significant reduction in seizure frequency (Engel Classification II). As expected, HS is often not seen on histological exam of resected tissue in patients with TLE and normal MRI.

In summary, invasive ictal EEG recordings can provide additional and, at times, important information, although they are mostly concordant to non-invasive recordings. In our study, the information obtained from the invasive ictal recordings extended the neo-cortical resection in five patients, who otherwise would have received a standard ATL resection and precluded two from receiving surgery (28.0%). Therefore, this study may provide some useful information to both clinicians and patients as to the yield of invasive ictal recordings in the pre-surgical evaluation of patients with intractable TLE and normal MRI of the brain.

Conflicts of interest

All authors have none to declare.

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REFERENCES

1. Hauser WA, Hwsdorffer DC. *Epilepsy: Frequency, Causes and Consequences*. New York: Demos Press; 1990.
2. Cockerell OC, Johnson AL, Sander JW, Hart YM, Goodridge DM, Shorvon SD. Mortality from epilepsy: results from a prospective population-based study. *Lancet*. 1994;344: 918–921.
3. Semah F, Picot MC, Adam C, et al. Is the underlying cause of epilepsy a major prognostic factor for recurrence? *Neurology*. 1998;51:1256–1262.
4. Stephen LJ, Kwan P, Brodie MJ. Does the cause of localisation-related epilepsy influence the response to antiepileptic drug treatment? *Epilepsia*. 2001;42:357–362.
5. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med*. 2000;342:314–319.
6. Engel Jr J. Surgery for seizures. *N Engl J Med*. 1996;334: 647–652.
7. McIntosh AM, Kalnins RM, Mitchell LA, et al. Temporal lobectomy: long-term seizure outcome, late recurrence and risks for seizure recurrence. *Brain*. 2004;127(Pt 9):2018–2030.
8. Spencer SS, Berg AT, Vickrey BG, et al. Initial outcomes in the multicenter study of epilepsy surgery. *Neurology*. 2003;61:1680–1685.
9. Salanova V, Markand O, Worth R. Temporal lobe epilepsy surgery: outcome, complications, and late mortality rate in 215 patients. *Epilepsia*. 2002;43:170–174.
10. Spencer SS, Williamson PD, Bridgers SL, et al. Reliability and accuracy of localization by scalp ictal EEG. *Neurology*. 1985;35:1567–1575.
11. Foldvary N, Klem G, Hammel J, et al. The localizing value of ictal EEG in focal epilepsy. *Neurology*. 2001;57:2022–2028.
12. Tonini C, Beghi E, Berg AT, et al. Predictors of epilepsy surgery outcome: a meta-analysis. *Epilepsy Res*. 2004;62: 75–87.
13. Spencer SS, Berg AT, Vickrey BG, et al. Predicting long-term seizure outcome after resective epilepsy surgery: the multicenter study. *Neurology*. 2005;65:912–918.
14. Cascino GD, Trenerry MR, So EL, et al. Routine EEG and temporal lobe epilepsy: relation to long-term EEG monitoring, quantitative MRI, and operative outcome. *Epilepsia*. 1996;37:651–656.
15. Cendes F, Li LM, Watson C, et al. Is ictal recording mandatory in temporal lobe epilepsy? Not when the interictal electroencephalogram and hippocampal atrophy coincide. *Arch Neurol*. 2000;57:497–500.
16. Gilliam F, Bowling S, Bilir E, et al. Association of combined MRI, interictal EEG, and ictal EEG results with outcome and pathology after temporal lobectomy. *Epilepsia*. 1997;38:1315–1320.
17. Chung JM, Kumar S, Soss JR, et al. How important are ictal recordings in pre-surgical evaluation for MTLE? *Neurology*. 2003;60(suppl 1):A260.
18. Stefan H, Pawlik G, Bocher-Schwarz HG, et al. Functional and morphological abnormalities in temporal lobe epilepsy: a comparison of interictal and ictal EEG, CT, MRI, SPECT and PET. *J Neurol*. 1987;234:377–384.
19. Baulac M, Saint-Hilaire JM, Adam C, et al. Correlations between magnetic resonance imaging-based hippocampal sclerosis and depth electrode investigation in epilepsy of the mesiotemporal lobe. *Epilepsia*. 1994;35:1045–1053.
20. Cascino GD, Jack Jr CR, Parisi JE, et al. Magnetic resonance imaging-based volume studies in temporal lobe epilepsy: pathological correlations. *Ann Neurol*. 1991;30:31–36.
21. Cendes F, Andermann F, Gloor P, et al. MRI volumetric measurement of amygdala and hippocampus in temporal lobe epilepsy. *Neurology*. 1993;43:719–725.
22. Spencer SS, McCarthy G, Spencer DD. Diagnosis of medial temporal lobe seizure onset: relative specificity and sensitivity of quantitative MRI. *Neurology*. 1993;43:2117–2124.
23. Scott CA, Fish DR, Smith SJ, et al. Presurgical evaluation of patients with epilepsy and normal MRI: role of scalp video-EEG telemetry. *J Neurol Neurosurg Psychiatry*. 1999;66:69–71.
24. Schiller Y, Cascino GD, Sharbrough FW. Chronic intracranial EEG monitoring for localizing the epileptogenic zone: an electroclinical correlation. *Epilepsia*. 1998;39:1302–1308.
25. Cascino GD, Trenerry MR, Sharbrough FW, et al. Depth electrode studies in temporal lobe epilepsy: relation to quantitative magnetic resonance imaging and operative outcome. *Epilepsia*. 1995;36:230–235.
26. Holmes MD, Born DE, Kutsy RL, et al. Outcome after surgery in patients with refractory temporal lobe epilepsy and normal MRI. *Seizure*. 2000;9:407–411.
27. 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;42:883–888.
28. Sylaja PN, Radhakrishnan K, Kesavadas C, et al. Seizure outcome after anterior temporal lobectomy and its predictors in patients with apparent temporal lobe epilepsy and normal MRI. *Epilepsia*. 2004;45:803–808.
29. Bell ML, Rao S, So EL, et al. Epilepsy surgery outcomes in temporal lobe epilepsy with a normal MRI. *Epilepsia*. 2009;50:2053–2060.
30. Engel Jr J, Van Ness PC, Rasmussen TB. Outcome with respect to epileptic seizures. In: Engel Jr J, ed.. In: *Surgical Treatment of the Epilepsies*. New York: Raven Press; 1993: 609–621.
31. Spencer SS, Sperling MR, Shewmon DA. Intracranial electrodes. In: Engel Jr J, Pedley , eds. In: *Epilepsy: A Comprehensive Textbook*. Philadelphia: Lippincott-Raven Publishers; 1997.
32. Spencer SS. Depth electroencephalography in selection of refractory epilepsy for surgery. *Ann Neurol*. 1981;9:207–214.
33. Schiller Y, Cascino GD, Sharbrough FW. Chronic intracranial EEG monitoring for localization of the epileptogenic zone: an electroclinical correlation. *Epilepsia*. 1998;39:1302–1308.
34. Binnie CD, Elwes RDC, Polkey CE, et al. Utility of stereoencephalography in preoperative assessment of temporal lobe epilepsy. *J Neurol Neurosurg Psychiatry*. 1994;57:58–65.
35. Elwes RDC, Binnie CD, Polkey CE. Normal magnetic resonance imaging and epilepsy surgery. *J Neurol Neurosurg Psychiatry*. 1999;66:3.

36. Diehl B, Luders HO. Temporal lobe epilepsy: when are invasive recordings needed? *Epilepia*. 2000;41(suppl 3): S61–S74.
37. Lau T, Miller T, Klein T, Benbadis S, Vale F. Temporal lobe surgery in medically refractory epilepsy: a comparison between populations based on MRI findings. *Seizure*. 2014;23:20–24.
38. Immonen A, Jutila L, Muraja-Murro A, et al. Long-term epilepsy surgery outcomes in patients with MRI-negative temporal lobe epilepsy. *Epilepsia*. 2010;51:2260–2269.