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Invasive EEG studies in tumor-related epilepsy: When are they indicated and with what kind of electrodes?

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Summary

Patients with tumor-related epilepsy (TRE) represent an important proportion of epilepsy surgery cases. Recently established independent negative predictors of postoperative seizure outcome are long duration of epilepsy, presence of generalized tonic–clonic seizures, and incomplete tumor resection. In temporal lobe cases, additional hippocampectomy or corticectomy may further improve outcome. Invasive electroencephalography (EEG) recordings (IEEG) may be indicated to guide the resection by defining eloquent cortex (EC) or to determine the extent of potentially magnetic resonance imaging (MRI)–negative epileptogenic tissue. In fact, invasive recordings are reportedly used in up to 10% of patients who are undergoing epilepsy surgery for TRE. Following careful consideration of the concepts underlying epilepsy surgery, the current use of IEEG, and the predictors of outcome in extratemporal and temporal tumors in TRE, we postulate the following> (1) In patients with extratemporal TRE, IEEG is necessary only if the MRI lesion (and if feasible a rim around it) cannot be completely resected because of adjacent or overlapping EC. In these cases, EC should be mapped to determine its relationships to the lesion, the irritative, and seizure-onset zones in order to maximize the extent of the lesionectomy. (2) In patients with nondominant temporal TRE, data suggest that if epileptogenic tumors (ETs) are encroaching on mesial temporal structures, if epilepsy duration is long, and seizures are frequent and disabling, these structures should be included in the resection. (3) In patients with dominant temporal TRE, we suggest leaving the mesial structures in place if they are functionally and structurally intact and to consider resecting these structures only if they are structurally and functionally abnormal. There is insufficient evidence justifying the use of IEEG to define the extent of the epileptogenic zone in such cases. This should be reserved for cases where an initial lesionectomy has failed.

KEY WORDS: Long-term epilepsy-associated tumors, Stereotactic EEG, Subdural grids, Glioneural tumors, Epilepsy surgery.

Cerebral tumors, especially low grade tumors, are associated with epilepsy in >50% of cases. About 30% of patients with tumor-related epilepsy (TRE) are pharmacoresistant and therefore good candidates for presurgical diagnosis and epilepsy surgery. Although TRE is usually lesional and resection borders are mostly well defined, a need for invasive electroencephalography (IEEG) studies is seen in up to 10% of cases according to TRE literature (Ozlen et al., 2010; Bulacio et al., 2012). Herein, we consider the concepts and evidence behind the use of IEEG in TRE to come up with a paradigm of when IEEG should be used and for which clinical questions an approach with stereotactic depth electrodes (stereo-EEGs) or subdural grid electrodes or a combination of depths and grids may be more advantageous.

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Conceptual Considerations

The concept of a symptomatic, irritative, ictal-onset, and epileptogenic lesion is helpful in considering which of these zones are best defined by which technique and how they are related to one another in TRE and predictive of the epileptogenic zone (Rosenow & Lüders, 2001). The epileptogenic lesion in TRE is usually detected with

excellent sensitivity and well defined by magnetic resonance imaging (MRI). However, glioneuronal tumors in particular may be associated with focal cortical dysplasia (FCD), which is not infrequently MRI negative (Prayson et al., 1993; Diehl & Lüders, 2000; Im et al., 2002). The irritative zone (IZ) and seizure-onset zone (SOZ) as well as the symptomatogenic zone (SZ) are defined during video-EEG (VEEG) monitoring (by EEG (IZ and SOZ) and video-analysis (SZ). These three zones are usually considered to be closely related to the epileptogenic zone (EZ), the region of cortex that can generate epileptic seizures and which, by definition, needs to be completely removed or disconnected to allow postoperative seizure freedom.

The eloquent cortex (EC) on the other hand is usually defined by functional MRI (fMRI), magnetoencephalography (MEG), or direct mapping with subdural or stereo EEG, or by repeated testing during awake resection. Invasive electrodes can be used to define IZ, SOZ, and also EC. In patients with TRE with single lesions the main questions are the relationship of the EL to EC or EZ. This relationship can be quite variable. At times there may be more than one lesion or MRI-negative dual pathology and noninvasive VEEG may not allow clarification of which lesion is epileptogenic (situation A6 in Fig. 1).

Complete resection of the EZ is the main aim of epilepsy surgery. Because most long-term epilepsy-associated tumors (LEATs according to Luyken et al., 2004) show little if any progression, theoretically each of the depicted situations in Figure 1 results in a different resection strategy. This suggests that it might be highly relevant to clarify the exact spatial relationship of the different zones in question in each case using IEEG as necessary.

If IEEG is used in TRE, subdural electrodes would preferentially be used whenever the EC and the EL are near the brain surface (e.g., Fig. 1B,D1). Stereo-EEG and depth electrodes on the other hand will be used in situations where EL and/or EC are located deeply and inaccessible to subdural grids (Fig. 1C,D2). Another aspect to consider when choosing subdural grid electrodes versus Stereo-EEG is the significantly higher rate of complications associated with the former (Hamer et al., 2002; Onal et al., 2003; Wong et al., 2009; Wellmer et al., 2012; Vale et al., 2013).

It has been reported that epileptogenic tumors can be associated with a relatively widespread IZ and SOZ, frequently extending beyond the lobe and even the hemisphere harboring the tumor (Hamer et al., 1999). However, evidence from case reports shows that even independent contralateral seizure onset as demonstrated by stereo-EEG does not exclude long-term seizure freedom after lesionectomy restricted to the ipsilateral side (Lüders, 2013; Fig. 2).

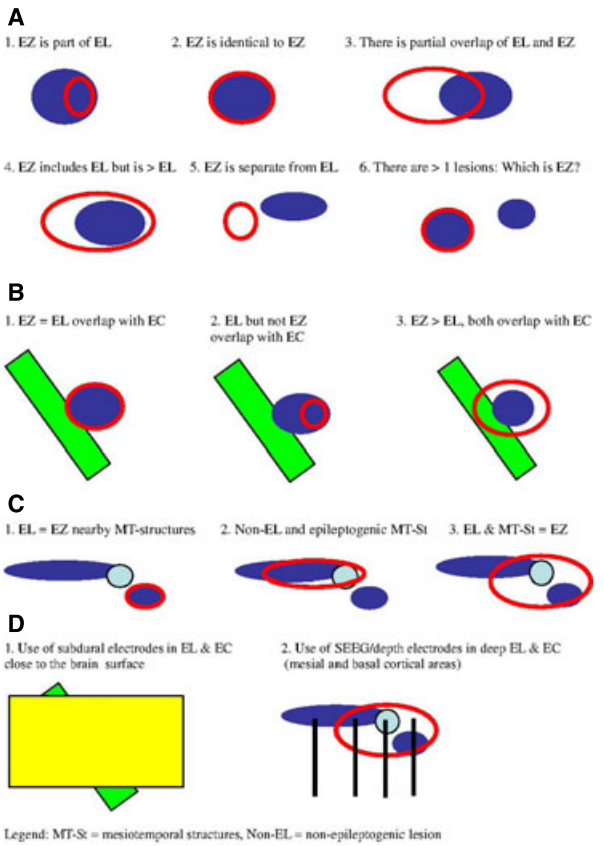

Figure 1.
Possible relations between the epileptogenic lesion (EL, blue) and (**A**) the epileptogenic zone (EZ, red, as indicated by IZ and SOZ), and (**B**) the eloquent cortex (green). (C) Possible relations of EL, EZ, and mesial temporal structures. (D1) Use of subdural electrodes (yellow) to delineate EL and EC in lesions near the surface. (D2) Use of stereo-EEG (black) in EL near the mesial temporal structures.

Current Use of Invasive EEG Studies in TRE

To determine if these conceptual considerations are relevant for clinical practice, we review the current clinical use of IEEG in the literature. A large series describing the use of IEEG in one surgical program over a decade (1998–2008) was recently published by Bulacio et al. (2012). In total, 406 IEEG procedures were performed, 70% of the procedures in adult patients. Thirty-one (9.2%) of the 336 patients who underwent resection and had a follow-up of >1 year were patients with TRE. In univariate analysis, tumor as etiology was a positive predictor of better seizure outcome ($p = 0.02$), with 58% of patients with TRE remaining seizure-free postoperatively. This finding is in line with a meta-analysis of

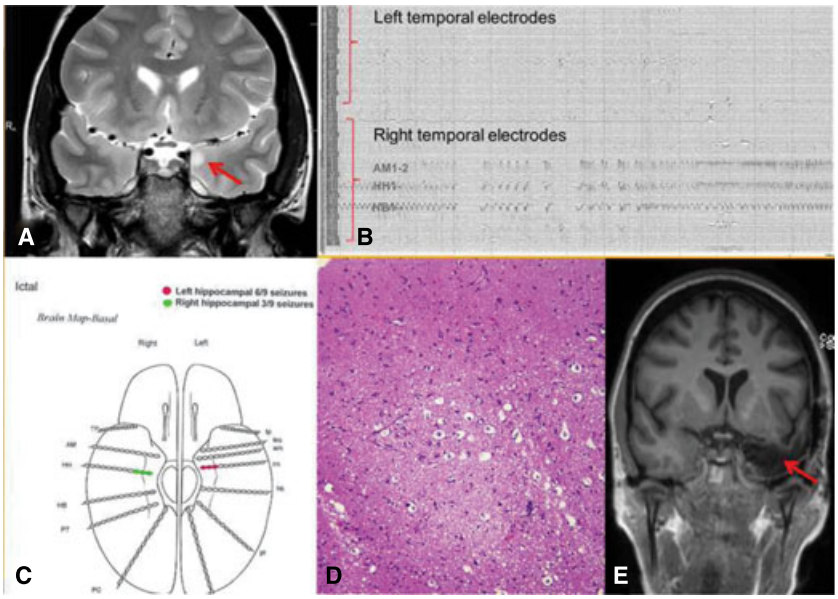

Figure 2.
Patient with (**A**) left mesial temporal glioneuronal tumor with (**B**) right hippocampal seizures who underwent a bilateral stereotactic EEG (SEEG) evaluation because of a bitemporal epilepsy confirmed by SEEG studies to show independent seizures arising from both mesial temporal lobes (**C**). Histopathology confirmed a glioneuronal tumor and International League Against Epilepsy (ILAE) classification type IIIb (**D**). The patient's coronal T_1-weighted postoperative MRI (**E**) shows complete tumor resection. She has been seizure-free for >18 months (Courtesy Hans Lüders, UH Case Medical Center, Cleveland, OH, U.S.A.).
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lesional versus nonlesional epilepsy cases showing that overall, the odds of being seizure-free after surgery were 2.5 times higher in patients with lesions on MRI or specific findings on histopathology (odds ratio [OR] 2.5, 95% confidence interval [CI] 2.1, 3.0, $p < 0.001$, Tellez-Zenteno et al., 2010). Another predictor for better seizure outcome was mapping of eloquent cortex as primary indication for IEEG evaluation (Bulacio et al., 2012). We suspect that there was extensive overlap between the two groups and that cortical mapping was the likely primary indication in many of the TRE cases.

Ozlen et al. (2010) reported the surgical results of a series of 52 patients with LEATs (28 dysembryoplastic neuroepithelial tumors [DNETs] and 25 gangliogliomas) and suggested that invasive EEG studies are generally not necessary unless there is a risk of destruction of EC. In this series, invasive EEG studies were deemed necessary in four cases (8%) with tumor close to either the central or Broca's areas. In these cases lesionectomy alone provided satisfactory results. Therefore, the main indication was to map EC in order to determine whether or not a complete lesionectomy could be safely performed. Alternative techniques such as fMRI have been recommended to map EC (Cataltepe et al., 2005). Even without the explicit use of invasive EEG recordings, results are still favorable, with 79% of patients with DNET or ganglioglioma remaining free of disabling seizures 2 years after surgery (Rydenhag et al., 2013).

Predictors of Postoperative Seizure Outcome

Positive predictors of a good (Engel class I, including patients with auras) postoperative seizure outcome include duration of epilepsy of <1 year at the time of surgery (OR 9.5), gross total resection (OR = 5.3), and the absence of generalized tonic–clonic seizures (OR = 2.5, Englot 2012a,b). In one meta-analysis, Englot et al. (2012b) added that: "Furthermore, tailored resection with hippocampectomy plus corticectomy conferred additional benefit over gross-total lesionectomy alone, with 87% of patients achieving seizure freedom (OR = 1.82, 95% CI: 1.23-2.70)". Overall, extended resection with hippocampectomy and/or corticectomy over gross-total lesionectomy alone significantly predicted seizure freedom (OR 1.18, 95% CI 1.11–1.26). Age <18 years and mesial temporal location also prognosticated favorable seizure outcome in patients with temporal lobe tumors (Englot et al., 2012a, b). This observation is corroborated by results of Minkin et al. (2008) who reported that "in 4 of 15 children with temporal DNTs, the lesionectomy alone failed to control seizures. These results could be explained by the wider

epileptogenic zone. … For children with temporal DNTs not invading the amygdalohippocampal complex, extensive presurgical evaluations seem indicated."

From these data together it appears that early gross total resection of the tumor is most important for seizure outcome. In patients with extratemporal tumors, invasive cortical mapping to exactly delineate eloquent cortex versus the epileptogenic tumorous lesion may be helpful in achieving the goal of gross tumor resection (Ozlen et al., 2010). On the other hand, in patients with temporal lobe tumors, the resection of additional cortical and/or hippocampal tissue may contribute to a more favorable seizure outcome (Minkin et al., 2008; Englot et al., 2012a,b).

Discussion

Despite evidence that LEAT may be associated with or partly consist of focal cortical dysplastic tissue, which in turn may be invisible on MRI, surgical outcome data suggest that postoperative seizure freedom depends largely on gross total resection of the MRI lesion (and in some temporal lobe cases with additional hippocampectomy and or corticectomy). The question of whether or not IEEG using subdural grid and/or depth electrodes is indeed helpful in identifying additional epileptogenic tissue and directing the resection has not been systematically studied. It has been shown that the IZ is more extensive in TRE as compared to other lesions such as hippocampal sclerosis, and can extend to the contralateral side (Hamer et al., 1999). Evidence from instructive cases indicate that independent contralateral seizure onset during an stereo-EEG investigation does not exclude long-term seizure freedom following exclusively ipsilateral epilepsy surgery in patients with TRE (Fig. 2). Therefore, the relevance of a precise definition of IZ and SOZ by IEEG for generating an operative hypothesis regarding the exact localization and extension of the epileptogenic zone may be relatively low in TRE, and at this point, it might be more appropriate to reserve the indication to do IEEG for patients who are not rendered seizure-free by the initial resection (Brogna et al., 2008). On the other hand, clear delineation of eloquent cortex in the vicinity of the EL according to the literature can help allow complete resection and thereby contribute to postoperative seizure outcome.

Conclusions

We conclude that: (1) In patients with extratemporal TRE, IEEG is necessary only if the MRI lesion (and if possible a rim around it) cannot be completely resected because of adjacent or overlapping EC. In this case EC should be mapped in relation to the lesion in order to clarify if a complete lesionectomy can be performed and to avoid postoperative deficits. (2) In patients with nondominant temporal TRE data suggest that if epileptogenic tumors are nearby or involve mesial temporal structures and if epilepsy duration is long and seizures are frequent and disabling, these structures should be included into the resection. (3) In patients with dominant temporal TRE we would suggest leaving the mesial structures in place if they are functionally and structurally intact and to consider resecting these structures only if they are abnormal. There is insufficient evidence justifying the use of IEEG to define the extent of the epileptogenic zone in such cases. This should be reserved for cases where an initial lesionectomy failed.

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Disclosures

The authors report no conflicts of interest. The authors confirm that they have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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