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Intracranial EEG analysis in tumor-related epilepsy: Evidence of distant epileptic abnormalities

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HIGHLIGHTS

- In most patients with TRE, at least part of SOSz lies distant from the tumor.
- Resection of the brain tumor plus SOSz results in excellent seizure outcome.
- On iEEG, interictal spikes are most abundant and sharpest in the peritumoral region.

ABSTRACT

Objective: In patients with tumor-related epilepsy (TRE), surgery traditionally focuses on tumor resection; but identification and removal of associated epileptogenic zone may improve seizure outcome. Here, we study spatial relationship of tumor and seizure onset and early spread zone (SOSz). We also perform quantitative analysis of interictal epileptiform activities in patients with both TRE and non-lesional epilepsy in order to better understand the electrophysiological basis of epileptogenesis.
Methods: Twenty-five patients (11 with TRE and 14 with non-lesional epilepsy) underwent staged surgery using intracranial electrodes. Tumors were outlined on MRI and images were coregistered with post-implantation CT images. For each electrode, distance to the nearest tumor margin was measured. Electrodes were categorized based on distance from tumor and involvement in seizure. Quantitative EEG analysis studying frequency, amplitude, power, duration and slope of interictal spikes was performed.
Results: At least part of the SOSz was located beyond 1.5 cm from the tumor margin in 10/11 patients. Interictally, spike frequency and power were higher in the SOSz and spikes near tumor were smaller and less sharp. Interestingly, peritumoral electrodes had the highest spike frequencies and sharpest spikes, indicating greatest degree of epileptic synchrony. A complete resection of the SOSz resulted in excellent seizure outcome.
Conclusions: Seizure onset and early spread often involves brain areas distant from the tumor.
Significance: Utilization of epilepsy surgery approach for TRE may provide better seizure outcome and study of the intracranial EEG may provide insight into pathophysiology of TRE.

1. Introduction

About 30–50% of patients with brain tumors present with seizures (van Breemen et al., 2007). In patients with intrinsic low-grade gliomas and glioneuronal tumors, the incidence is

Abbreviations: TRE, tumor-related epilepsy; SOSz, seizure onset and seizure spread zone; qEEG, quantitative electroencephalography; iEEG, intracranial EEG; MRI, magnetic resonance imaging; CT, computerized tomography.

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>90% (Kurzwelly et al., 2010). Seizures can increase morbidity in these patients and hence, there is growing interest in developing methods, which achieve optimal seizure control along with aggressive tumor removal. Complete removal of the lesion results in better seizure control compared to subtotal excision, though not everyone becomes seizure-free (Chang et al., 2008; Englot et al., 2011). In fact, in a comprehensive systematic review of the literature of seizure outcomes in 1181 patients with tumor-related epilepsy (TRE) across 41 studies, only 43% of patients were seizure-free after subtotal tumor resection whereas 79% achieved seizure freedom following gross-total lesionectomy (Englot et al., 2012). Recently, use of tailored resection with intraoperative electrocorticography to identify electrographic abnormalities around tumor margin often yielded improved seizure outcome (Mikuni et al., 2006; Seo and Hong, 2003; Sugano et al., 2007). The prevailing thought is that the immediate peritumoral area shows the most frequent epileptiform activity, possibly due to microscopic tumor infiltration (Mikuni et al., 2006; Rassi-Neto et al., 1999; Weber et al., 1993). Most studies have focused on temporal lobe lesions and electrocorticography restricted to brief intraoperative period done under anesthesia, which may itself alter epileptiform activity.

In the present study, we combined brain tumor resection with a tailored two-stage surgical approach of prolonged extraoperative intracranial EEG (iEEG) monitoring used for epilepsy surgery to investigate the spatial relationship between the tumor and the SOSz. We also performed quantitative EEG (qEEG) analysis of interictal spikes in patients with TRE and compared the spike parameters to patients without lesions.

2. Methods

2.1. Patient data and EEG recordings

A total of 25 patients with intractable epilepsy, 11 patients with a primary brain tumor (metastatic brain tumors and suspected high-grade gliomas were excluded) and 14 patients with non-lesional epilepsy undergoing epilepsy surgery during the same time period, were included in the study. All patients underwent a two-staged surgery with implantation of arrays of subdural grids and depth electrodes. Prolonged (usually 5 days) extraoperative iEEG recordings were obtained using a 128-channel Harmonie system (Stellate Inc., Montreal, Canada) and reviewed using a referential montage with frontopolar midline (FPz) scalp electrode as a reference.

On the basis of previously published work, each electrode was labeled by an experienced electroencephalographer (AKS) in one of three categories: (i) seizure onset (earliest sustained EEG changes distinct from background rhythms associated with the patient's habitual seizures); (ii) early seizure spread (ictal EEG pattern propagation recorded consistently within 10 s of electrographic seizure onset); or (iii) non-epileptogenic zone (non-EZ, electrodes not included in seizure onset or early spread category) (Asano et al., 2003; Spencer et al., 1992). The electrodes identified as seizure onset or seizure spread were, together, labeled as SOSz. If there were variations in electrode involvements between different seizures, electrodes from all habitual seizures involved in seizure onset or first 10 s of spread were included as SOSz electrodes.

Ten-minute iEEG segments were selected by the same encephalographer from periods of quiet wakefulness at least six hours after a clinical seizure. These samples were then processed with our validated interictal spike detection algorithm (see below) (Barkmeier et al., 2012b). All surgical procedures were performed by the same epilepsy/brain tumor neurosurgeon (SM). The patients with TRE were divided into two groups based on histopathology (infiltrating versus non-infiltrating tumors). Seizure and tumor outcome data were collected at one and two years following surgery. Informed consent was obtained from all subjects for protection of patient information and tissue collections and approved by the Wayne State University Human Investigation Committee.

2.2. qEEG analysis of ictal and interictal EEG

A validated spike detection algorithm was used initially to mark the interictal spikes of each 10-min iEEG sample (Barkmeier et al., 2012b). Obvious artifacts were removed from the data by manually reviewing marked spikes. Custom MATLAB scripts (MathWorks Inc., Natick, MA) were then used for extraction of data related to each interictal spike. The average frequency of spikes was calculated for each electrode. Each spike was further analyzed by dividing it into two half-waves with midpoint being the peak (Fig. 1A). To calculate the amplitude, duration, and slope of each half-wave, 80 ms of data were searched on either side of the peak to find the lowest value in that range designated as the spike's trough. Distance to the peak value was used to calculate duration while the difference in voltage was used to calculate amplitude. Values preceding trough to peak were defined as 'amp1' and 'dur1' while values from peak to succeeding trough were defined as 'amp2' and 'dur2'. Slope was calculated as amplitude/duration for each half-wave.

2.3. Three-dimensional reconstructions and tumor segmentation

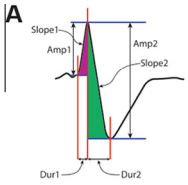
To investigate the spatial relationship between the tumor and electrographic activity, we generated 3D reconstructions of each patient's brain, including segmentation of the tumor and overlay of the intracranial electrodes. To achieve this, we utilized Visual C++ and OpenGL to implement an image analysis and visualization software system consisting of the following modules: (i) co-registration of multimodality image volumes (Hu and Hua, 2009; Muzik et al., 2007; Zou et al., 2007); (ii) partial differential equation-based deformable model for 3D-structure segmentation (Hua and Qin, 2004); (iii) subdural grid mapping and rendering; and (iv) surface mapping and composited visualization (Hua et al., 2008; Zou et al., 2009). Cortical surfaces were generated from preoperative volumetric T1-weighted MR images using the automated cortical surface reconstruction software (BrainSuite09, http://neuroimage.usc.edu/neuro/BrainSuite) (Shattuck and Leahy, 2002). Post-implantation skull X-rays and/or CT scans were co-registered with the pre-implantation MRI to localize precisely the intracranial electrodes on the patient's 3D-brain reconstruction. In all cases, accuracy of electrode localization was manually confirmed by matching gyral patterns between intraoperative photographs and 3D-reconstructions. Using these images, color-coded heat maps were generated on the cortical surface with a green-to-red color scale corresponding to various electrical parameters of interictal spikes including spike frequency, amplitude, duration, and slope. In addition, each electrode was identified based on its seizure category as either SOSz (seizure onset and early seizure spread) or non-EZ.

2.3.1. Measurement of distance between tumor margin and electrodes

To compute the distance between the electrodes and the tumor border, tumor margins were manually outlined on preoperative FLAIR images. The marked points in each slice were connected with Bspline-based interpolation to form a closed contour defining the tumor border within the MRI slice. After all slices were marked, the contours were combined to generate a 3D-mask defining the tumor. The final tumor surface was reconstructed using the Marching Cubes algorithm, which was saved in the original MRI coordinate space (Lorensen and Cline, 1987).

To calculate distance, the location of each electrode was identified on the 3D-brain surface. Our algorithm then determined the

A



B

Electrode Type	Epileptogenic zone (EZ)												Non-epileptogenic zone (Non-EZ)				Total no of electrodes
Group	Seizure Onset				Seizure Spread				Total EZ				Non-EZ				
Non-lesional	104				122				226				886				1112
Lesional	Tumoral	Peritumoral	Non-tumoral	Total	Tumoral	Peritumoral	Non-tumoral	Total	Tumoral	Peritumoral	Non-tumoral	Total	Tumoral	Peritumoral	Non-tumoral	Total	693
	27	14	21	64[†]	48	17	20	87[‡]	75	31	41	151	146	108	275	542[*]	

Fig. 1. Quantitative EEG analysis of spike parameters (A). Each spike was divided into two half-waves at the peak. Eighty milliseconds of data were searched on either side of the peak to find the lowest value and designated the spike's trough. Distance to the peak value was used to calculate duration (Dur) and the difference in voltage was used to calculate amplitude (Amp). The parameters preceding trough to peak were defined as Amp1 and Dur1. The parameters succeeding trough were defined as Amp2 and Dur2. Slope was calculated as amplitude/duration for each half-wave (slope1 = Amp1/Dur1; slope2 = Amp2/Dur2). The number of intracranial electrodes in patients with tumor-associated and non-lesional epilepsy is outlined in (B).[†]including 2 electrodes without distance measurement; [‡]including 2 electrodes without distance measurement; [*]including 13 electrodes without distance measurement.

shortest distance from the tumor border to the electrode. Then, the Euclidean distance between them was computed in millimeters. Electrodes were grouped based on this measured distance into "tumoral" (<1.5 cm from tumor margin), "peritumoral" (1.5–2.5 cm from tumor margin) and "non-tumoral" (>2.5 cm from tumor margin) groups.

2.4. EEG and Statistical analysis

Using MATLAB, data from qEEG analysis was aggregated and averages were generated for amplitude, duration, slope, and frequency of interictal spikes for each channel in each patient. Spike power was calculated by multiplying spike frequency with spike amplitude (power = frequency * amplitude). Because the magnitudes of these interictal spike parameters varied widely between patients, we first normalized each of these parameters to 100% within each patient before combining data from all patients. For example, the channel with the highest spike frequency in each patient was set to 100% and all other channels were scaled proportionately to this value. Data from all 11 lesional patients were then aggregated for subsequent statistical analysis and compared to aggregate data from all 14 non-lesional control patients. The datasets in this study do not follow the normal distribution, so non-parametric statistics were used, such as the Kruskal–Wallis test for 3-way comparisons and the Wilcoxon rank-sum test for 2-way comparisons. A p value less than 0.05 was considered significant.

3. Results

The majority of patients in the study had extratemporal or multilobar seizure onset (6/11 in TRE and 9/14 in non-lesional group). Isolated mesial temporal lobe seizure onset was observed in only 3 patients in TRE group and 2 patients in non-leisonal group. In eleven patients with TRE, a total of 693 intracranial electrodes were implanted (mean: 63; range: 38–96); while in the non-lesional group, a total of 1112 intracranial electrodes were implanted (mean: 79; range: 16–112) (Fig. 1B). In the TRE group, 151 were identified as SOSz electrodes (seizure onset = 64, seizure spread = 87). In addition, out of a total of 676 electrodes where distance to tumor could be measured, 221 were classified as tumoral, 139 as peritumoral, and 316 as non-tumoral. Distance could not be measured for 17 electrodes in patients with TRE due to technical reasons (4 SOSz and 13 non-SOSz). In the non-lesional group, out of 1112 electrodes, 226 were identified as SOSZ electrodes (seizure onset = 104, seizure spread = 122) and 886 as non-EZ.

3.1. The SOSz is often distant from the tumor margin

Eleven subjects had seizures associated with primary brain tumors (see Table 1 for details). In these patients, arrays of subdural recording electrodes were placed both above and around the margins of the tumors taking into consideration findings of all presurgical evaluation to define the spatial relationship between the tumor and epileptic zones (Fig. 2). In 10 of the 11 primary brain tumor patients, all or part of the SOSz was more than 1.5 cm from the nearest tumor margin (Figs. 3 and 4A–H). Furthermore, nearly half of the electrodes (72/151 = 47.7%) labeled as SOSz were greater than 1.5 cm from the tumor margin (peritumoral + non-tumoral electrodes).

3.2. Surgical outcome

A gross total resection was achieved in all lesional cases with no evidence of tumor recurrence in all but one case at one-year following surgery. Of these 11 patients with TRE, 10 were seizure-free (Engel Class I) at one-year, while one patient with incomplete resection of the SOSz involving Broca's area continued to seize (Engel Class III). At two-years, 8/9 surviving patients remained seizure-free. The 2 other patients also remained seizure-free before dying from tumor recurrence 18 months after surgery. In the non-lesional group, 13 patients underwent resective surgery (one with multifocal SOSz had no resection). Ten patients had complete resection of the SOSz. Eight patients had good outcome (Engel Class I and II) at 2-years after surgery. All three patients with incomplete excision of the SOSz had poor seizure control. Of the remaining two patients with complete resection of SOSz and poor seizure outcome, one had diffuse hemispheric cortical dysplasia and other had nonspecific histopathologic findings of gliosis.

3.3. Changes in interictal spike parameters versus distance from tumor

Quantification of interictal spike parameters has been used as a tool in two-stage epilepsy surgery to help better characterize the SOSz and understand epileptogenesis. Most common spike parameters studied include frequency of interictal spikes, spike amplitude, duration, slope and power (Asano et al., 2005,2003; Hufnagel et al., 2000; Rakhade et al., 2007,2005). To study interictal spikes in TRE, quantitative spike parameters were plotted as function of distance from the tumor margin (Fig. 4I–L). Interestingly, spike frequency and power tend to peak in the "peritumoral" area (between 1.5 and 2.5 cm from tumor margin), while duration is the shortest. Wilcoxon ranks-sum tests comparing tumoral (<1.5 cm from tumor margin) to peritumoral areas shows that peritumoral regions have significantly higher spike frequencies ($p = 0.046$) and power ($p = 0.024$), but shorter spike durations ($p = 0.002$). When comparing tumoral areas to distant non-tumoral areas of the same brain (>2.5 cm from tumor margin), electrodes within the tumoral area had significantly lower amplitudes ($p < 0.001$) and less steep slopes ($p = 0.001$) than non-tumor electrodes.

Table 1
Patient demographics.

Patient			Seizure-related information			Tumor-related information			
No.	Age (yrs)	Sex	Seizure onset	Complete resection of epileptogenic zone	Outcome at 1 and 2 years*	Infiltrating Tumor	Tumor Location	Histopathology	Outcome at 2 years
1	54	M	T	Y	1,1	Y	A	Low-grade oligodendroglioma with astrocytic component	No recurrence
2	40	M	Multi	Y	1,–	Y	A	Anaplastic oligoastrocytoma	Recurrence - Died
3	35	M	F	N	3,3	Y	A	Low-grade oligodendroglioma	No recurrence
4	22	M	T	Y	1,2	Y	A	Ganglioglioma	No recurrence
5	47	F	T§	Y	1,1	N	A	Dysembryoplastic neuroepithelial tumor	No recurrence
6	42	F	Multi	Y	1,–	Y	A	Anaplastic oligoastrocytoma with a nodule of sarcoma	Recurrence - Died
7	36	F	F	Y	1, 1	Y	A	Anaplastic oligoastrocytoma	No recurrence
8	44	M	F	Y	1, 1	Y	A	Low-grade oligoastrocytoma with focal anaplasia	No recurrence
9	38	F	T§	Y	1, 1	N	E	Dermoid tumor	No recurrence
10	50	M	Multi	Y	1, 1	N	E	Epidermoid tumor	No recurrence
11	40	F	T§	Y	1, 1	N	E	Typical meningioma, transitional type	No recurrence

* Engel classification of seizure outcome. T = Temporal.
§ T = medial temporal only, F = Frontal, Multi = Multilobar.

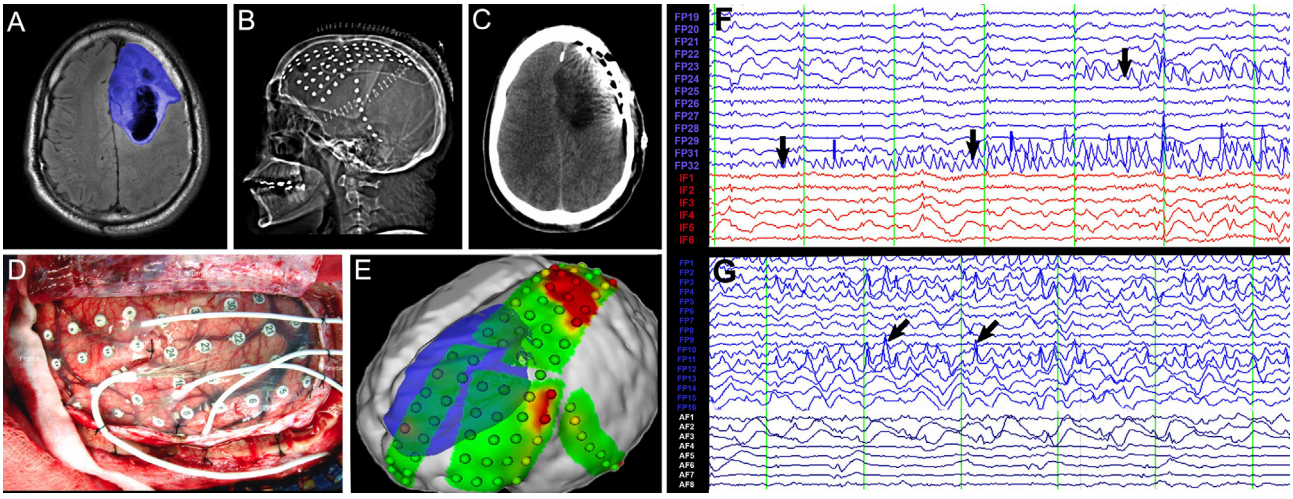


Fig. 2. Illustrative case with 3D reconstruction, tumor segmentation, with overlay of electrophysiological data. Axial MR image with tumor segmentation shown in blue (A). Co-registration and precise localization of the intracranial electrodes on the patient's 3D reconstruction was achieved using postimplantation imaging (B and C) and intraoperative photomicrographs (D). 3D brain reconstruction with tumor rendering (blue) overlaid with intracranial electrodes (circles) were generated with color-coded heat maps using a green-to-red color scale (E). Intracranial EEG recording used to define the SOSZ (F, ictal onset and spread, arrows) and interictal EEG used for quantitative EEG analysis (G, interictal spike, arrows). Note the spatial relationship between interictal spike frequency and tumor (E, red electrodes). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Limiting the comparison groups to only SOSz electrodes either within the tumor area (<1.5 cm) or distant from the tumor margin (>2.5 cm) still yielded significantly lower amplitudes ($p = 0.001$) and more shallow slopes ($p = 0.010$) for the electrodes within the tumor, suggesting that this observation (smaller, sharper spikes) is a result of the tumor proximity itself, rather than a potential difference in the intrinsic epileptogenic potential of the cortex.

3.3.1. Comparative analysis of qEEG parameters of interictal spikes from SOSzs in lesional and non-lesional patients

Next, we performed comparative analysis of qEEG parameters of interictal spikes in TRE and non-lesional epilepsy groups to understand effects of the tumor itself independent of epileptogenicity of the cortex. The interictal spike parameters between the 11 patients with TRE and the 14 non-lesional patients were analyzed. In both groups, SOSz electrodes had higher spike frequencies and higher spike powers compared to the non-EZ electrodes (in the lesional group: $p = 0.003$ for spike frequency and $p = 0.002$ for spike power; in the non-lesional group: $p < 0.001$ for both spike frequency and power).

Directly comparing interictal spike parameters in SOSzs between TRE and non-lesional patients groups showed that SOSzs in non-lesional patients had slightly steeper spike slopes ($p = 0.010$), but yielded no significant differences in spike frequency ($p = 0.110$), power ($p = 0.200$), amplitude ($p = 0.180$), or duration ($p = 0.063$). Finally, a 3-way Kruskal–Wallis test (non-parametric ANOVA) was used to compare quantitative spike parameters of SOSz electrodes in non-lesional patients to those in tumor patients either within the tumor area (<1.5 cm) or distant from the tumor (>2.5 cm). Although SOSzs that lie outside the tumor area did not differ from non-lesional SOSzs, SOSz electrodes within the tumor area showed significantly lower frequencies, lower powers, lower amplitudes, and less steep slopes than SOSz of non-lesional patients and SOSz electrodes that lie distant from tumor (frequency $p = 0.022$; power $p = 0.030$; amplitude $p = 0.001$; duration $p = 0.180$; slope $p = 0.003$). For spike frequency, tumoral SOSz electrodes had lower frequency than non-lesional SOSz electrodes, but did not significantly differ from non-tumoral SOSz electrodes. For spike power, tumoral SOSz electrodes had lower power than non-tumoral SOSz electrodes, but did not

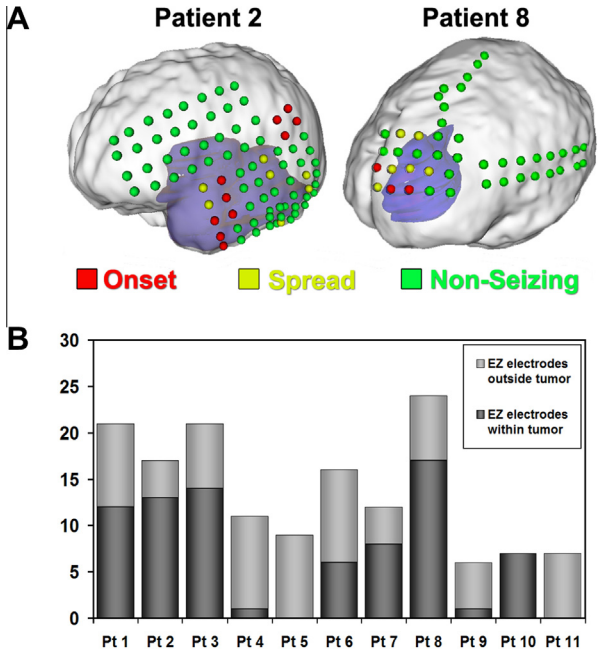


Fig. 3. Spatial relationship between tumor and seizure onset and spread zone. (A) 3D rendering with tumor segmentation and overlay of subdural grid electrodes. Each electrode is identified based on its seizure category into either as seizure onset (red), early seizure spread (yellow), or non-epileptogenic zone (green). (B) Histogram of all 11 patients with TRE showing percentage of electrodes labeled as epileptogenic zone (SOSz) (seizure onset and early seizure spread electrodes combined) within (<1.5 cm) or outside (>1.5 cm) the tumor margin. Of note, all SOSz electrodes were within the tumor margin in one patient (#10), whereas they were all outside of the tumor in two patients (#5 and #11). Overall, nearly half (47.7%) of the SOSz electrodes were >1.5 cm from the tumor margin. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

significantly differ from non-lesional SOSz electrodes. These results fit with prior tests which showed that tumor areas have significantly lower amplitudes and slopes than non-tumor areas.

3.3.2. Infiltrating tumors show wider area of abnormality

While the sample size in the present study is small, we asked whether any significant differences were apparent between patients with infiltrating tumors ($n = 7$) compared to those with non-infiltrating tumors ($n = 4$). All seven patients with infiltrating tumors had both seizure onset electrodes and SOSz (seizure onset or spread) electrodes more than 1.5 cm from the tumor margin. Three of four patients with non-infiltrating tumors had some SOSz electrodes distant from the tumor.

Interictal spike parameters were compared between patients with infiltrating tumors and with non-infiltrating tumors to see whether interictal analysis could provide any additional insight into the dissemination of tumor cells. Comparison of tumor electrodes (<1.5 cm from margin) between the two groups showed that regions near the main body of the tumor were very similar, with the only difference being that infiltrating tumors had interictal spikes with less steep slopes than non-infiltrating tumors. Comparisons of both peritumoral electrodes (1.5–2.5 cm from margin) and non-tumoral electrodes (>2.5 cm from margin) between patients with infiltrating or non-infiltrating tumors, however, showed extensive differences in interictal spike parameters. Patients with infiltrating tumors had significantly higher spike frequency and spike power than non-infiltrating tumor patients in both peritumoral and non-tumoral electrodes.

4. Discussion

4.1. TRE overview

Adults with new-onset seizures commonly harbor brain tumors. Certain types of tumors, such as dysembryoplastic neuroepithelial tumors, oligodendrogliomas, and gangliogliomas are more likely to present with TRE (Japp et al., 2013; Mittal et al., 2008; Ruda et al., 2012). Conversely, high-grade neoplasms generally have a lower prevalence of TRE. One possible explanation is that development of seizures is a process that evolves over time and may not become operational in a rapidly-growing tumor. It is also plausible that pathophysiological and functional characteristics intrinsic to the neoplasm (other than its growth potential) may be responsible for TRE (Buckingham et al., 2011; Pallud et al., 2013).

4.2. Management of TRE

4.2.1. Conventional approach

Gross total removal of the MRI-visible lesion is a standard goal in the treatment of primary brain tumors. Hence, most patients with TRE undergo neurosurgical intervention primarily for tumor removal. Likewise, focal cortical resection is a proven and established treatment option for patients with pharmacoresistant epilepsy including those with continued seizures following tumor resection (Rosenow and Menzler, 2013; Sweet et al., 2013). Though patients may not fulfill all the criteria of medical intractability at the time of neuro-oncological surgery, surgical intervention for tumor clearly provides an opportunity to address the associated seizures at the same time. It is also known that tumor resection by itself may not provide optimal seizure freedom in a sizeable proportion of patients (Englot et al., 2011; Ghareeb and Duffau, 2012). In a systematic literature review of 1181 patients with epilepsy related to low-grade temporal lobe brain tumors, only 79% of patients were seizure-free after complete lesionectomy (Englot et al., 2012). These patients might benefit from additional removal of SOSzs at the time of initial tumor surgery (Mittal et al., 2010, 2013).

4.2.2. Proposed approach to TRE

Our study demonstrates that the SOSz is often situated at a significant distance from the tumor margin. Electrodes up to 1.5 cm beyond the MRI-defined tumor margin were included as tumoral electrodes in order to take into account tumor cell infiltration and wider resection margins (especially in non-eloquent regions). This provided more stringent criteria to define the SOSz remote from tumor (beyond 1.5 cm), which is unlikely to be removed as oncologic gross total resection. The only way to precisely identify the SOSz beyond the tumor margin prior to removal of the tumor so that the epileptic tissue can be potentially resected along with the tumor is to institute a staged-epilepsy surgery approach with intracranial monitoring.

We also noted that the SOSz is often eccentric to one side and not located circumferentially around the tumor. Hence, additional resection of extra-tumoral epileptic tissue does not require a wide margin of resection but rather focal excision of the SOSz. Simply widening the tumor resection margin non-selectively may not adequately remove the entire SOSz and may also be detrimental to neurological outcome.

One of the advantages of a two-staged approach is that it can provide a more detailed characterization of the tissue at the time of removal as it pertains to electrophysiological characteristics, such as seizure onset zone, seizure propagation zone and to identification of non-spiking cortex. One can further study these

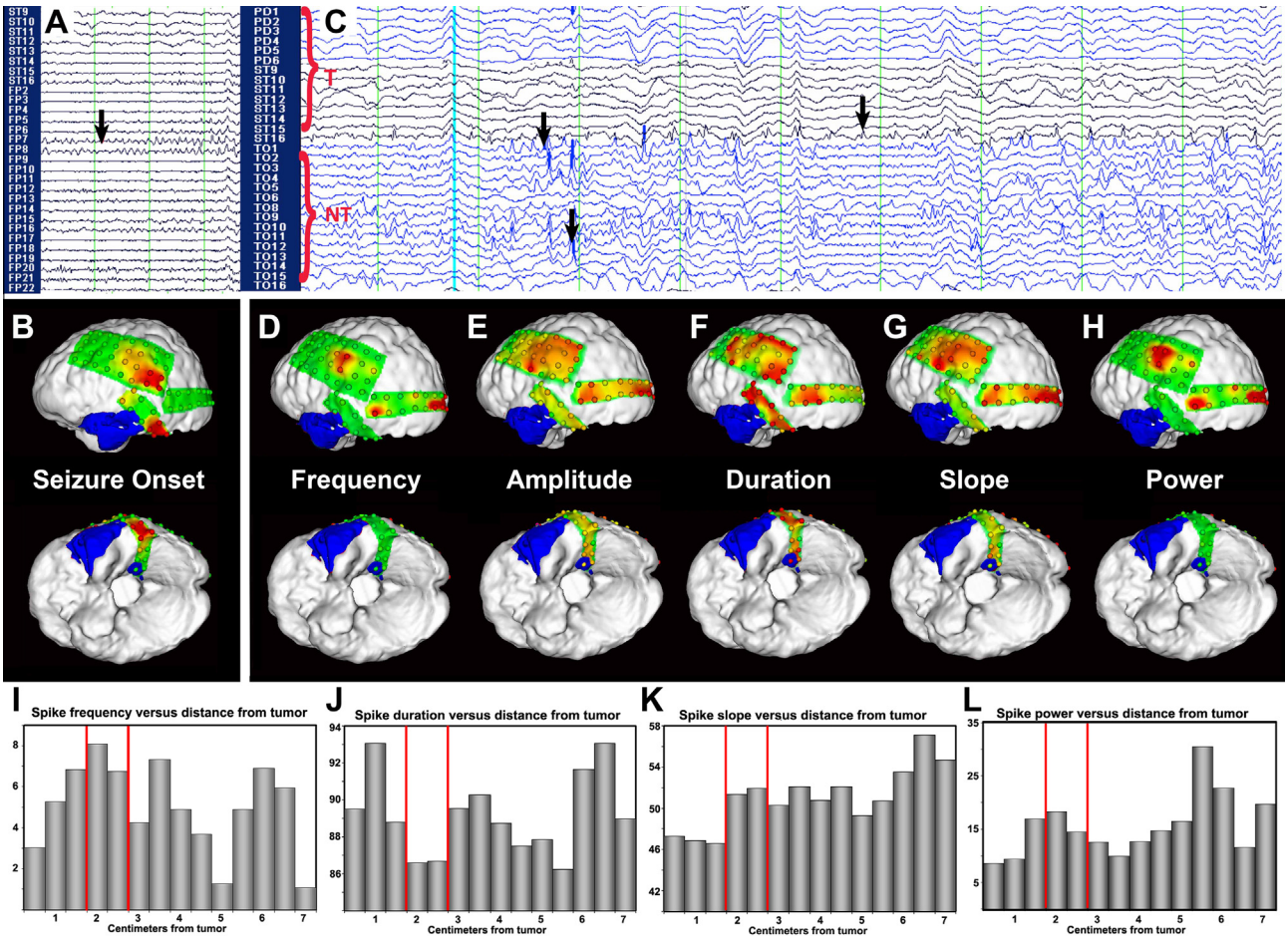


Fig. 4. Spatial relationship between tumor and electrophysiological data. Intracranial EEG recording from select channels showing seizure onset (A, arrow). Color-coded heat maps showing part of the seizure onset zone (red) is distant from tumor (outlined in blue) (B). Selected channels of interictal EEG used for quantitative EEG analysis of interictal spikes (C) including spike frequency (D), amplitude (E), duration (F), slope (G), and power (H). (Electrodes identified as T were close to the tumor, while NT were distant from the tumor, arrows identify interictal epileptiform activity). Quantitative EEG analysis of interictal spike parameters in relationship to distance from tumor margin were as follows: spike frequency (I) and power (L) tend to peak in the "peritumoral" area (1.5–2.5 cm from the tumor margin), while spike duration (J) is the shortest and spike slope (K) did not differ. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

well-defined tissues in variety of ways to advance our understanding of focal TRE (Mittal et al., 2013).

4.3. Interictal EEG analyses in TRE

The second aspect of this study is the quantitative analysis of interictal epileptiform activity. Interestingly, the main difference in interictal spike morphology noted in the study was smaller amplitude of the spikes from the areas in close proximity to the tumor. Though the frequency of the spikes remained high in these areas, individual spikes were smaller and narrower. This was even more pronounced in patients with infiltrating tumors. When compared to discrete tumors, both peritumoral and non-tumoral electrodes in patients with infiltrating tumor had significantly higher spike frequency and spike power, but spikes had lower amplitude and slope. This may represent more widespread epileptogenicity, given that we previously found higher spike frequency and spike power to be characteristic changes in SOSz electrodes. Potentially, this could suggest a wider infiltration of tumor cells or tumor-induced cortical dysfunction, in view of the fact that electrodes overlying tumors had similar characteristics with interictal spikes exhibiting less steep slopes and amplitudes than those in non-tumoral electrodes. The interictal spike amplitude depends upon population of neurons depolarizing in unison. Therefore, lower spike amplitude may be due to effects of the tumor cell infiltration effectively "diluting" the number of depolarizing neurons under the electrode or affecting layer-specific differences in neuronal networks as recently described in both human data and in a rat model of interictal spiking (Barkmeier et al., 2012a; Beaumont et al., 2012).

Correlating these parameters with tumor histopathology, tumor infiltration, and other in depth *in vitro* studies from the tissue obtained in a similarly systematic way may provide additional valuable information. Our long-term goal is to establish a set of electrophysiological parameters to better define the SOSz and to guide tumor resection margin. This knowledge could lead to improved seizure and tumor outcomes. Additional prospective studies with larger numbers of patients with TRE (harboring a variety of histologic tumor types) is needed to determine whether long-term recordings can lead to reduced seizure as well as tumor recurrence.

Conflict of interest

None of the authors has any conflict of interest to disclose.

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