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Selection of Candidates for Epilepsy Surgery and Non-Invasive Methods During Presurgical Evaluation, Present Protocols and General Approach

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To address the general approach to epilepsy surgery in terms of patient selection and evaluation, one needs to first outline the kinds of epilepsy surgery in current use, and the correlates of successful outcome. Then, the non-invasive evaluation can be described as a series of studies designed to elucidate the factors associated with success. Finally, non-invasive evaluation cannot be fully described without some reference to invasive evaluation, indicating when it is required, and how it is used. These factors place the general evaluation and patient selection into perspective.

Epilepsy surgery in 1996 includes a variety of types of operations, the most common and preferred of which are the resective procedures. These may involve temporal or extratemporal resection, resection of a lesion associated with uncontrolled epilepsy, or modified hemispherectomy. Resective procedures are the preferred approaches to medically uncontrolled epilepsy because, through removal of epileptogenic region, they offer the possibility of cure. There are, however, other operations which can be considered for refractory epilepsy, including mainly the disconnection procedures. Corpus callosum section is the prototype of disconnection, and aims to prevent secondary generalization. Subpial transection might also be considered a disconnection procedure, is gaining momentum, and is applied to individuals in whom the region identified as being responsible for seizure onset is not resectable because of its functional importance. Finally, stimulation procedures are also occasionally used for the treatment of medically uncontrolled epilepsy. At this time only vagal nerve stimulation is in this class. Disconnection and stimulation rarely cure seizures, and are generally regarded as choices only when resection is not possible. The selection of the procedure depends entirely on localization and definition of the extent of the epileptogenic region. Particularly, we seek to define whether the epileptogenic region is extensive or restricted, unifocal or multifocal, and whether it involves functional regions of the cortex.

Broadly stated, the selection criteria for resective procedures include [1-3]:

1. Seizures should continue despite optimal medical management including major drugs in monotherapy and polytherapy. Included are usually phenytoin, carbamazepine, barbiturate, valproate, as well as the recent additions of lamotrigine, gabapentin, and in some countries vigabatrin.

2. Although each drug and each combination need not be used, it should be clear after variety of medication trials over approximately two years that the seizures remain uncontrolled such that they interfere significantly with an individual's lifestyle. There is no specified number of seizures or frequency of seizures that qualifies an individual for this criterion, but rather the character of the seizures and the individual's lifestyle and how they interact with one another that determines whether and individual will be a candidate.

3. There are no additional medical conditions that would complicate or prevent the evaluation and successful rehabilitation of the individual. In the past, psychiatric conditions were thought to be a contraindication, but it is clear at this time that their presence is independent of the refractory

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placing what we will say into perspective. Lest it not be evident after this extensive discussion about the importance of pathology and etiology, it should be emphasized from the outset that localization of the epiloptogenic region is critical in the selection of the procedure and of its success[2,5,6,31-35]. Some demonstration of localized electrical excitability is always required in this process, because this aspect alone defines the epileptogenic region. The extent to which this EEG localization is pursued, however, can be modified by the presence of concordantly localized abnormalities of structure and function, which as we have noted demonstrate important correlates with success.

In epilepsy surgery patient evaluation, aspects of the investigation include electrical localization, structural assessment, functional study, and historical information. These are generally performed in a series of phases such that the non-invasive evaluation precedes invasive evaluation, and hopefully is sufficient in a certain number of patients. The "phase 1" constitutes the non-invasive evaluation and incorporates aspects of each of the electrical, structural, functional, and historical components. The history and neuropsychological examination are supplemented by MRI, SPECT and PET, and audiovisual EEG monitoring in phase 3 and surgery in phase 4. I will address each of the components of the non-invasive evaluation in phase 1 first, and then proceed to put those together into a coherent picture of present day protocols for selection of patients for epilepsy surgery.

With regard to the history, certain features stand out as predictive and important. As we mentioned, early risk factors including trauma, infection, or seizures occurring under the age of four have been associated with later appearance of mesial temporal sclerosis. Since this is highly correlated with success after temporal lobe resections, it is an important feature of the history to be sought in any epilepsy surgery candidate. Other items of the history are equally important for their negative prognostic value: trauma and infection after the age of four are often associated with multifocal seizure onset which may disqualify an idividual from consideration of (at least resective) epilepsy surgery. Adult onset seizures without a prior contributory history are often due to neoplasms or vascular lesions, but can be due to developmental abnormalities. These individuals may still be candidates for epilepsy surgery, although localization tends to be more difficult.

In the neuropsychological evaluation, certain deficits are localizing to particular cerebral areas. For example, left frontal lesions produce deficits in new learning, while right frontal lesions are associated with abnormalities in attention and performance IQ. The dominant temporal lobe is important for verbal processing and verbal IQ, while the non-dominant temporal lobe is important for recognition of faces, melody, and performance IQ. Posterior lesions produce deficits in visual construction and perception. The neuropsychological evaluation often reveals multiple abnormalities despite the presence of a single, localized area of epileptogenesis. It therefore must be interpreted in the context of all the other findings.

The intracarotid amobarbital test is a part of the neuropsychological evaluation. It produces temporary unilateral cerebral anesthesia during which one can test memory and language function of the contralateral hemisphere independently. This provides a measure of memory competency in each temporal lobe, which is significant not only for the definition of abnormal function, but also for selection of candidates for temporal lobe resections; memory competency must be present in the contralateral temporal lobe prior to any temporal lobe resective procedure.

We turn now to the electrical components of non-invasive patient evaluation for epilepsy surgery. With surface EEG, 10/20 positions are supplemented by anterior temporal and sphenoidal electrodes. We attempt to record the EEG interictally in all sleep states, as well as ictally during multiple spontaneous seizures. Clinical and EEG correlation is then performed. Medication withdrawal may be necessary to record the specified number of ictal events for examination and analysis. The criteria for interpretation of the surface EEG have undergone some evolution over recent years. As we noted earlier, some demonstration of localized electrical excitability in the contemplated area of resection is required, and this may be satisfied by the surface EEG in certain patients. Ideally, local-

ization of the ictal event includes a localized rhythmic discharge at 5-8 Hz medial temporal abnormalities; faster or slower frequency rhythmic discharges are seen in extratemporal seizure onset locations. Interictal spikes, however, may be multifocal (which is common with posterior foci), bilateral and independent (which is common in medial temporal lobe epilepsy), or absent completely (which is most common in frontal lobe epilepsy).

The published criteria for medial temporal localization by scalp EEG have included 90% or more anterior temporal interictal discharges (maximal on referential montages is the sphenoidal, T1, F7, F9 electrodes or corresponding contralateral positions) with adequate sampling (at least 50 interictal epileptiform discharges) [36,37]. On the ictal scalp EEG, for localization of medial temporal lobe epilepsy, anterior rhythmic theta or alpha discharge lasting for at least 10 seconds that occurs within 30 seconds of seizure onset, but not necessarily before the clinical seizure, is considered localized because of its high correlation with successful outcome [26-28]. Electrical localization with scalp EEG may be sufficient, provided that the epilepsy syndrome can be confirmed with other components of the non-invasive evaluation, as we will specify.

Scalp EEG recorded during the seizure is concordant with the location of MRI abnormality in approximately 30-40% of patients with hippocampal sclerosis, developmental lesions, or tumors, and only discordant in 9-13%. More often, however, the scalp ictal EEG is unlocalized; this includes half of the patients in all of the pathological groups. This observation defines the frequent need for electrical localization from the interictal scalp EEG, confirmed by other localizing studies, in order for non-invasive evaluation to suffice. Overall, 40-50% of patients have successful electrical localization by scalp EEG for purposes of surgery [1]. (Although many more have apparently localized spikes or seizure onset, the fact that the ictal and interictal may conflict reduces the number in whom localization is sufficient). Surface EEG accuracy is reportedly poor for defining the lobe of seizure onset, but is better for lateralization[38]. False lateralization is sometimes seen with large structural lesions.

The clinical seizure patterns are important, not only to correlate with the EEG, but also to establish localization. Earliest manifestations are critical, but the evolution of clinical features can also be useful in providing a presumptive localization of seizure onset location. Review of multiple spells for stereotypy is essential. However, it must be recalled that multiple seizure types may arise from a single epileptogenic region due to variable propagation into other cortical regions. This is most common with posterior onset seizures, which may propagate variably to temporal and frontal lobes. It is helpful to review the characteristics of seizures arising in various cortical regions. Familiarity with these patterns can be useful to establish non-invasive localization [25, 39-44].

Temporal lobe seizures tend to occcur at a frequency of 3-10 per month, last 1-5 minutes, and begin and terminate gradually. They are commonly preceded by psychic or epigastric warnings and have bland clinical manifestations that are often composed of staring and arrest of activity or speech. Oral or gesticular automatisms are common, and may involve the upper more frequently than the lower extremities. Often a contralateral upper extremity dystonia is seen. Postictal confusion, as well as aphasia when the seizure arises in the dominant temporal lobe, are also common features of the temporal lobe seizure.

In contrast, frontal lobe seizures tend to occur much more frequently in this refractory group, from 10-50 or even more per month, or multiple seizures on a single day. These seizures are much briefer than the temporal lobe variety, sometimes lasting only 15 seconds. They begin and terminate abruptly, often without postictal confusion. An aura is often present but may be non-specific.

The seizures are characterized by prominent motor manifestations including tonic, clonic, or dystonic activity which may occur bilaterally or unilaterally and are often accompanied by loud vocalization and a tendency to secondary generalization. Frontal lobe seizures tend to be bizarre and dramatic, but they are also stereotyped, aiding diagnosis and distinction from psychogenic events.

Finally, parietal and occipital lobe seizures may begin with a sensory or visual aura; dizziness is a common complaint at the beginning of occipital lobe seizures. The simple partial sensory component of these seizures may be either positive or negative including loss of vision or spots, tingling or numbness. Subsequently, these seizures may propagate along infra-Sylvian (to the temporal lobe) or supra-Sylvian routes (to the frontal lobe) and assume the characteristics of temporal and frontal lobe seizures. Without the simple partial sensory and visual phenomena being reported by the patient, it can be difficult to predict the true parietal or occipital origin of these seizures.

Structural imaging is a component of non-invasive evaluation that has assumed singular importance in the past decade. MRI is the preferred structural imaging procedure in epilepsy, and can detect abnormalities in 50% or more of chronic epilepsy patients. Quantitative volumetric analysis and T2 relaxometry of the hippocampus have raised the yield for detecting the structural correlate of mesial temporal sclerosis to 85% or higher. MRI is also capable of detecting more than 95% of the neoplasms and vascular lesions associated with chronic refractory epilepsy [15,45]. Although the yield is somewhat less, there is increasing ability to detect developmental abnormalities associated with refractory epilepsy in any cortical region. There is also a high (80-90%) correlation of the location of the imaging abnormality with the region of epileptogenesis, making these findings even more significant [46]. In 5-10% of patients considered for epilepsy surgery, however, "dual" pathology, often the combination of hippocampal atrophy with another structural lesion, are present. Since either of these structurally abnormal areas (or another!) may be the source of the epilepsy, the other features of the non-invasive evaluation assume more importance in those situations[47]. Extensive structural lesions may also be present without clear implications for which part of the abnormal area is epileptogenic. In the interpretation of MRI abnormalities, it should also be mentioned that intense seizure activity can occasionally cause transient focal increases in T2 signal. Not all structural abnormalities seen in epilepsy patients, even solitary ones, are the region where seizures begin. It is worth emphasizing again that despite the virtual revolution in epilepsy diagnosis and management wrouht by MRI, electrical abnormalities define the epileptogenic region in the final diagnosis.

Qualitative MRI results were reviewed in 809 patients who were reported in the literature with EEG localization in order to assess its accuracy with regard to the epileptogenic region as defined by EEG [48]. In patients with temporal lobe abnormalities on MRI, 87% were concordant with the EEG and only 5% were discordant. In patients with extratemporal MRI structural abnormalities, only 55% were concordant with EEG, while 25% were discordant. 366 (almost a third) of these patients had unlocalized MRIs; in this group 69% had temporal EEG abnormalities and 10% extratemporal EEG abnormalities. This data establishes the conclusion that although MRI can be very sensitive, particularly in the medial temporal region, it is sometimes discordant with the EEG definition of the epileptogenic region. That is, MRI is sometimes incapable of demonstrating the structural correlate of the epileptogenic area. When quantitative methods are used to define hippocampal region abnormalities on MRI, the yield is improved only slightly.

Functional imaging methods include those for imaging blood flow and metabolism. For blood flow, SPECT or PET can be used, but usually SPECT. Interictal reduction in blood flow in the region of epileptogenesis is reported in 50-80% of chronic, refractory epilepsy patients. Of 539 patients reported in the literature with interictal SPECT blood flow imaging and EEG results, interictal SPECT defined a temporal region of hypoperfusion in more than half of the patients; in nearly 80% of these, it was concordant with temporal EEG abnormalities, and in 10% it was discordant. Of 65 reported patients with extratemporal regions of hypoperfusion demonstrated by SPECT, only 47% were concordant with the EEG, and 26% were discordant. Finally, 183 patients had no abnormalities on interictal SPECT; of them, more than half had temporal EEG abnormalities. These figures are roughly reminiscent of the finding on MRI. Thus, interictal SPECT study of blood flow will demonstrate a localized abnormality concordant with the EEG in many patients with

temporal lobe EEG abnormalities, but is certainly not uniformly successful; and is more often discordant with the EEG demonstrated region of epileptogenesis in individuals with extratemporal epilepsy. Interictal SPECT can be difficult to interpret because multiple interictal areas of hypoperfusion may be present; the zone of interictal hypoperfusion is often extensive, extending well beyond the zone of EEG and/or structural abnormality; and heterotopic gray matter may cause interictal hyperperfusion.

PET with fluorodeoxyglucose is used to image interictal metabolism in epilepsy. Over 90% of patients with mesial temporal sclerosis are reported to have interictal reduction in temporal metabolism, a much higher yield than for blood flow in this pathologic entity. Its accuracy is also quite good. Of 312 patients reported in the literature with EEG localization and PET results, PET defined a temporal region of hypometabolism in 205, of whom 95% were concordant with temporal EEG abnormality, with only three patients discordant. Of 32 patients with extratemporal hypometabolism, 56% were concordant with EEG localization. 75 patients had normal PET, about half of whom temporal EEG localization. Thus, PET had very high sensitivity for temporal lobe EEG abnormalities, and lower sensitivity in extratemporal regions.

We can contrast the three interictal imaging procedures. For temporal EEG abnormalities, PET has the highest sensitivity at 84%, with qualitative MRI at 55%, and SPECT at 66%. For extratemporal EEG abnormalities, SPECT has the highest sensitivity, while MRI and PET have the lowest[48]. The question of what determines the differential between blood flow and metabolism in the epilepsies arises from this data. If one reviews the literature for patients with proven pathology of resected tissue and MRI, PET, and interictal SPECT results, we find that in mesial temporal sclerosis, the diagnoctic sensitivity (predictive value of a positive test result) is nearly 100% for MRI and PET, but considerably lower at 70% with interictal SPECT blood flow imaging. In contrast, in developmental lesions, interictal SPECT was somewhat superior in demonstrating abnormal flow in the region with a diagnostic sensitivity of 92% compared to 88% and for MRI and PET. MRI remains most sensitive to tumors. Viewed in this way, it is not the cortical area so much as the underlying anatomical and physiological process that determines the differential sensitivity of the various imaging techniques. Blood flow and metabolism appear to be uncoupled in mesial temporal sclerosis, a finding peculiar to that epileptogenic entity. They are more closely related in epilepsies associated with developmental lesions and tumors. This knowledge is useful in interpreting the imaging results[49].

Before I leave the non-invasive imaging evaluation, and in the context of the above observations, we should comment on the yield of PET and SPECT in epilepsy with normal MRI. This was examined, using the minimal patients reported in the literature. With normal MRI in developmental lesions, SPECT and PET can be abnormal in up 25%. It should be noted, however, that when PET was abnormal it was always concordant with the EEG localization, but when SPECT was abnormal (just as often), the abnormality was usually not in the temporal region. Therefore SPECT appears to be unreliable in this settings[49].

Ictal imaging has received much attention lately. SPECT can show areas of increased blood flow in the region of epileptogenesis. It is ideally suited for this application, to a greater degree than any other imaging technique, because the injected Technetium radioligands are bound on first pass through the brain, and no redistribution occurs for 3-4 hours. This enables one to make the injection during the seizure, and perform the scan several hours later when the patient is more cooperative. 108 patients have been reported in the literature with SPECT ictal imaging and EEG results. 80 were localized to the temporal lobe by the SPECT study, 93% of them concordant with EEG, while 16 were localized to extratemporal regions, 56% concordant with EEG. The diagnostic sensitivity to the epileptogenic zone was quite high, 90% for temporal regions and 81% for extratemporal[48,49].

Interpretation of ictal SPECT, however, can be problematic. Although injection of the HMPAO radioligand within 30 seconds of seizure onset shows diffuse temporal hyperperfusion in almost 100% of patients with temporal lobe epilepsy, and

is almost always consistent with EEG, the longer the delay for the injection the more difficult interpretation becomes. Rapid evolution of blood flow occurs, with medial temporal hyperperfusion lasting for 1-8 minutes, and lateral temporal hypoperfusion beginning shortly thereafter and lasting up to 20 minutes [50]. Our group has recently defined a similar evolution of changes in extratemporal epilepsy. It appears that when injection his made within 100 seconds of seizure onset, hypoperfusion in the region of epileptogenesis may be just as helpful in defining the location of seizure onset.

We can now contrast the diagnostic sensitivity and specificity in temporal and extratemporal regions of all the various imaging techniques, including interictal PET, interictal and ictal SPECT, and qualitative and quantitative MRI. Confirming previous observation, PET is the most sensitive of the interictal procedures in temporal lobe epilepsy, and ictal SPECT exceeds even that sensitivity at 90%; quantitative MRI is 70% effective and interictal SPECT, 66%. In extratemporal epileptogenic regions, ictal SPECT is again superior to any other method for imaging the localized region of epileptogenesis, while interictal SPECT is also more sensitive than PET or MRI.

We return to the principles of localization for epilepsy surgery in order to place these non-invasive techniques into perspective. Various combinations of these studies are considered necessary and sufficient for resective epilepsy surgery without intracranial or invasive study in a variety of protocols that have been developed. The goal is to achieve the most sensitive and specific non-invasive evaluation that will accurately predict the region of epileptogenesis. As we have stated many times, some electrical localization of the epileptogenic zone is required for resective epilepsy surgery; some patients will require intracranial EEG for that purpose. The requirements for surgical localization using non-invasive methods can be simply stated. First, we must demonstrate localized electrical excitability using ictal or interictal EEG recorded from the scalp, but without discordance. Second, we must demonstrate concordant localization of abnormal structure and/or function. No conflicting localization from any study can be accepted. Finally, we must be able to resect the region that has been so designated without the need for extraoperative mapping of functional cortical tissue. If these criteria are stasfied, surgery may proceed after non-invasive evaluation. In all other situations, invasive EEG is recommended.

The current protocols for invasive and non-invasive epilepsy surgery patient selection at our institution will illustrate these concepts more specifically. These protocols follow closely from the items in the preoperative evaluation that have been shown to correlate with success, and are modeled closely upon other prospectively validated non-invasive protocols for epilepsy surgery. For lesional epilepsy surgery, we require that a circumscribed lesion (usually representing a tumor or vascular lesion) be present on qualitative MRI analysis. We are willing to recommend resection based on non-invasive evaluation (using electrocorticography or pathology to define the margins of resection) provided that ictal or interictal scalp EEG is localized to the area of the lesion, neither is discordant with the location of the lesion, and the lesion is not adjacent to functional cortical areas that require extraoperative mapping. In all other situations, invasive EEG is pursued. For temporal lobe non-lesional epilepsy surgery, the protocols are more complicated and depend on the results of major and minor criteria. The major criteria utilized in these decisions include the ictal EEG localization, the interictal EEG localization, and MRI. The minor criteria include memory asymmetry on the WADA test, temporal hypoperfusion on SPECT, temporal hypometabolism on PET, significant hemisphere specific memory disturbance, and interictal anterior temporal slowing. Utilizing these criteria in non-lesional temporal lobe epilepsy, resection of a medial temporal structure can proceed with non-invasive evaluation that fulfills these criteria: no evidence from any study of extratemporal localization; all major criteria are localized to anterior temporal regions, or two major and two minor are localized to the anterior temporal region; no discordant localization is demonstrated; and memory is supported contrateraally. In all other situations, invasive EEG evaluation will be required for non lesional temporal lobe epilepsy surgery.

Sometimes temporal lobe seizures appear to arise

independently in either temporal lobe. In these situations, surgery may be recommended based on non-invasive evaluation also. In those cases, we require that an adequate sample of seizures has been recorded, that the intracarotid amobarbital procedures shows adequate contralateral memory, that there are no signs of extratemporal epilepsy, that more than 50% of seizures arise in the contemplated resected lobe, that an early risk factor was present and that hippocampal atrophy be present in the lobe contemplated for resection (both establishing "true" medial temporal epilepsy).

Finally, all patients with non-lesional extratemporal epilepsy require intracranial or invasive EEG evaluation. The criteria from the non-invasive study guide the sampling sites selected for the inserted electrodes. Ictal SPECT has become increasingly useful in this setting.

Before concluding, I would like to make some brief comments on intracranial study. Depending on the referral population, 20-50% of surgical candidates require invasive EEG. It's use has diminished, however, with our more sensitive and validated non-invasive evaluation. The locations of electrode placement are individualized, based on the non-invasive evaluation. Additional placements will consider likely propagation and homotopic sites. The number of electrodes is variable, up to 12 in any individual patient. The electrodes may be composed of depth electrodes, subdural strip electrodes, or subdural or epidural grids. They are all multicontact, MRI compatible electrodes that are used for chronic recording and can be combined as needed for optimal study[51,52]. In the interpretation, the interictal record is considered less important because of the common presence of multiple independent sites of spiking. True ictal onset in the medial temporal region often shows periodic high amplitude spikes at one per second, followed by a 10-20 Hz rhythm, this can be recorded with either hippocampal depth electrodes or subdural strip electrodes that reach the medial temporal region. Neocortical seizure onset is characterized by very high frequency onset at greater than 40 Hz with a superimposed or adjacent low frequency 5-10 Hz rhythmic discharge. The pattern of propagation is important in the final interpretation. The sampling restrictions of intracranial EEG always require its interpretation in the context of all other data [53-56].

Intracranial EEG has assumed importance in a variety of situations as defined by our patient protocols. One of the most common is the patient with bilateral hippocampal atrophy. We studied 53 patients who had volumetric MRI, intracranial EEG, and temporal lobectomy and found that five had bilateral hippocampal atrophy. Based on intracranial EEG, the seizures could arise in the most atrophic hippocampus or the less atrophic hippocampus. (Furthermore, not all patients with bilateral hippocampal atrophy had bilateral independent seizure onset.) With resections that were based entirely on the intracranial EEG study, four out of five patients with bilateral atrophy were completely cured of their seizures, and all had mesial temporal sclerosis. This underlines the importance of intracranial EEG in this kind of "dual pathology"[57].

Intracranial EEG is successful in localizing an area for resection in 75% of patients when based upon the previously described criteria. The risk of major complications remains approximately 2%. When intracranial EEG is used because of confusing or insufficient localization and it predicts successful surgery at a rate comparable to that obtained when patients are selected non-invasively.

One might ask what the predictive value of various non-invasive studies for the intracranial ictal localization is. Unfortunately, such studies can only be done using the most difficult group of patients who have been selected for intracranial study. In that group, quantitative MRI was the best predictor of the intracranially demonstrated medial temporal lobe seizure onset, but no individual non-invasive study or combination of two, was uniformly predictive of the results on intracranial study[48]. It should also be underlined that intracranial EEG itself does not uniformly predict pathology or surgical outcome in that difficult group of patients, and that our criteria for interpretation, while improving, are not complete, and our sampling sometimes inadequate.

Mapping can be done extraoperatively or intraoperatively. Extraoperative mapping with grids

allows superimposition of ictal localization on functional cortical regions in the area contemplated for resection, and can be a primary criterion for the performance of invasive EEG. In epilepsy surgery in the vicinity of sensory motor cortex, evoked potentials can be used intraoperatively instead. Language localization can sometimes be performed intraoperatively to avoid the use for invasive EEG, when the relation of this to ictal onset is not deemed to be critical.

In summary, these various localizing methods are combined in a variety of protocols using non-invasive (and sometimes invasive) criteria to select a surgical procedure in medically refractory epilepsy. If a single epileptogenic region is defined, resection is preferred (if it is considered safe), but the procedure may vary based on location and predicted substrate. In individuals who have multifocal seizure onset, it's important to exclude a single posterior epileptogenic zone with variable propagation; sometimes this requires invasive EEG. Patients with bilateral medial temporal lobe seizure onset are still considered candidates for resective surgery of the most dysfunctional temporal lobe [58], and hemispherectomy is considered if all of the multifocal regions of seizure onset occur in one hemisphere and if significant motor deficit is present. If multifocal seizure onset is present and seizures generalize frequently, callosotomy is an alternative, as is vagal nerve stimulation. In some patients seizure onset is unlocalized (despite non-invasive and invasive evaluation). In these situations, one can consider additional invasive study, callosotomy or vagal nerve stimulation.

In individuals who have a localized but unresectable region of epileptogenesis, if seizures generalize frequently, callosotomy is an option, as is subpial transection or vagal nerve stimulation.

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