Epilepsy surgery: eligibility criteria and presurgical evaluation

Philippe Ryvlin, MD, PhD; Sylvain Rheims, MD

Among the 50 to 60 million individuals suffering from epilepsy worldwide, up to one third might develop pharmacoresistance.[1] In a subset of this population, epilepsy surgery represents the optimal treatment option. However, the proportion of drug-resistant patients who could or should be offered a surgical treatment remains largely unknown, with estimates varying from 5% to 50% of all cases of drug-resistant epilepsies. This uncertainty reflects a lack of appropriate studies, and disagreements regarding the criteria that best define an epilepsy surgery candidate, as well as the major gap between the number

Epilepsy surgery has benefited from major advances during the last 20 years, thanks to the development of neuroimaging and long-term video-electroencephalographic (EEG) monitoring. However, it remains the case that only a small minority of potential epilepsy surgery candidates will have access to a comprehensive presurgical evaluation. Furthermore, this subset of patients are operated on after an average of 20 to 25 years of epilepsy duration. Among the various reasons that prevent many patients from benefiting from a timely presurgical evaluation, we need to emphasize the role of inaccurate information regarding eligibility criteria and lack of standardized practice. This review aims at providing an in-depth discussion of the current views regarding the definition of surgical candidates, and the role of the numerous investigations used in the presurgical evaluation of patients with drug-resistant epilepsy.

The eligibility criteria required to enter a presurgical evaluation in 2008 should be relatively liberal, provided that the patient suffers from disabling seizures unrelated to an idiopathic generalized epileptic syndrome, despite appropriate antiepileptic drug treatment. However, the decision as to whether or not to perform a presurgical evaluation must be individualized, and take into account the likelihood of meeting the patient's expectations in terms of outcome. These expectations need to be balanced with the apparent severity of the epileptic condition, the chance of achieving a successful surgical treatment, and the risk of a postoperative neurological, cognitive, or psychiatric deterioration.

The roles and specific features of the main types of presurgical investigations are reviewed.

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Author affiliations: Department of Functional Neurology and Epileptology, Neurological Hospital, CTRS-INSERM IDEE (Institut Des Epilepsies de l'Enfant et de l'adolescent), Hospices Civils de Lyon, INSERM U821, Université Claude Bernard Lyon 1, Lyon, France

Address for correspondence: Philippe Ryvlin, Unité 301, Hôpital Neurologique, 59 bd Pinel, 69003, Lyon, France
(e-mail: ryvlin@cermep.fr)

Selected abbreviations and acronyms

AED	*antiepileptic drug*
DA	*dopamine*
EEG	*electroencephalogram*
EZ	*epileptogenic zone*
GABA	*γ-aminobutyric acid*
MRI	*magnetic resonance imaging*
PET	*positron-emission tomography*
SPECT	*single photon-emission computed tomography*
TLE	*temporal lobe epilepsy*

of these potential candidates and that of patients that are actually operated on.[2]

Furthermore, the majority of patients who are eventually operated on are referred for surgery after an average of 20 to 25 years of epilepsy duration.[3,4] This delay is likely responsible for a significant number of avoidable seizure-related deaths, including drowning, motor vehicle accident, fatal status epilepticus (SE), and sudden unexpected death in epilepsy (SUDEP), the rate of which is about 1% per year in patients with drug-resistant epilepsy.[5] In addition, the longer the delay between the onset of drug-resistant epilepsy and surgery, the lower the chance of postoperative seizure freedom and improved socioprofessional outcome.[4,6,7] This issue is further aggravated by the 1- to 2-year waiting list for entering a presurgical evaluation program in the majority of epilepsy surgery centers.

Several reasons underlie the above situation, including the patients' and physicians' legitimate fear of a postoperative permanent neurological deficit, the frequently insidious course of chronic epilepsy,[8] the relatively low yield of long-term postoperative seizure freedom (~ 60% after 10 years of follow-up),[9] the paucity of randomized control trials (RCTs) demonstrating the efficacy of surgical therapy over antiepileptic drugs (AEDs),[10] the complexity and heterogeneity of surgical treatments, and the limited resources dedicated to the presurgical evaluation of epilepsy patients.

Some of these reasons can now be challenged. For instance, major safety progress has been made in the field of neurosurgery, with a risk of unexpected vascular or infectious complications resulting in a residual disabling neurological impairment of about 1% in experienced epilepsy surgery groups.[2,11] Thus, the risk of seizure-related death or serious injury in drug-resistant patients refusing epilepsy surgery (about 1% per year), is significantly higher than the major morbidity/mortality associated with surgical treatment (about 1% in total). The suboptimal yield of postoperative long-term seizure freedom must also be balanced with the much worse figures reported in patients who have not been operated on, only 5% to 14% of whom will achieve seizure remission.[12,13] Altogether, the available data in the literature strongly suggest that epilepsy surgery is significantly more efficacious than medical treatment.

Eligibility criteria for presurgical evaluation and epilepsy surgery

Patient selection for epilepsy surgery is a two-step procedure that first aims to identify potential surgical candidates who should benefit from a presurgical evaluation, and then to determine in each assessed individual whether the risk:benefit ratio for surgery is acceptable. Three main criteria must be fulfilled to enter the first step: (i) the patient (or his or her parents for young children and patients with intellectual impairment) needs to understand the objective of the presurgical evaluation and to agree on the possibility of a surgical treatment; (ii) the patient should suffer from disabling seizures despite appropriate medical therapy; and (iii) available imaging and electroclinical data should be consistent with the possibility of a surgically remediable epileptic syndrome.

The first criterion is minor, but should not be overlooked, since it often represents a limiting factor in patients who would otherwise be considered good surgical candidates. The second criterion relies on the definition of disability and drug resistance. The assessment of disability must take into account a number of objective parameters, such as seizure frequency and severity, AED side effects, and also the socioprofessional and familial impact of the disease, and the patient's subjective rating of his or her overall handicap. The patient's perception that his or her disability is worth taking the risk of a surgical treatment plays a major role in deciding to proceed to a presurgical evaluation. However, this judgment is not always based on realistic expectations of postoperative outcome, and thus needs to be balanced with the physician's more objective view of the risk:benefit ratio of epilepsy surgery. Regarding drug resistance, there is a general agreement to consider a patient medically refractory if two or more appropriately selected and managed AEDs failed to control his or her seizures.[14] Indeed, once a patient has not responded to the first two drugs, the likelihood of achieving sustained seizure freedom with any

other medical treatment is less than 5%.[15] A 2-year follow-up is also usually required to conclude on the presence of a refractory epilepsy in adult patients. However, shorter epilepsy duration can be accepted in epileptic children with catastrophic epilepsies.[2]

The third criterion to be considered, ie, the identification of a surgically remediable epileptic syndrome, has been classically defined as the presence of a symptomatic or cryptogenic localization-related epilepsy, whose suspected underlying epileptogenic zone (EZ) should be unique, and not overlapping with eloquent brain regions. However, important progress has been made in the field, allowing widening of the scope of epileptic syndromes amenable to surgery. These now include patients with various forms of symptomatic generalized epilepsies, such as infantile spasms associated with cortical dysplasia,[16,17] seemingly multifocal partial epilepsy related to tuberous sclerosis,[16,18] EZ involving eloquent areas,[19,20] Landau-Kleffner syndrome,[16] and patients combining a surgically remediable partial epilepsy and an idiopathic generalized epileptic syndrome with the hope of curing the former with surgery, allowing a more appropriate AED regimen to control the latter.[21] In addition, palliative surgical treatments, such as callosotomy and deep brain stimulation, can be proposed in patients with other forms of severe cryptogenic or symptomatic generalized epilepsies, including Lennox-Gastaut syndrome.[22]

To summarize, the eligibility criteria required to enter a presurgical evaluation in 2008 should be relatively liberal, provided that the patient suffers from disabling seizures unrelated to an idiopathic generalized epileptic syndrome, despite appropriate AED treatment. However, the decision as to whether or not to perform a presurgical evaluation must be individualized, and must take into account the likelihood of meeting the patient's expectations in terms of outcome. These expectations need to be balanced with the apparent severity of the epileptic condition, the chance of achieving a successful surgical treatment, and the risk of a postoperative neurological, cognitive, or psychiatric deterioration. The same questions arise once the presurgical evaluation has been completed, in order to decide on a surgical treatment, though the weight placed on each of the above parameters is likely to vary towards more stringent criteria (ie, more severe epilepsy, greater will of the patient to take the risk of surgery given a clear understanding of his or her individual prognosis, higher chance of achieving postoperative seizure freedom, lower risk of postoperative deterioration). The gap between eligibility criteria used for entering a presurgical evaluation and those applied to deciding on a surgical treatment determines the proportion of patients assessed for surgery who will be operated on, eventually. This proportion, together with the profiles of surgical candidates, largely varies between epilepsy surgery centers, as a function of their experience and culture. For instances, some centers focus on temporal lobe epilepsy (TLE) surgery whereas other develop specific expertise in catastrophic epilepsies of childhood, extratemporal partial epilepsies, cryptogenic cases, or operations in eloquent brain regions.

Presurgical evaluation

The primary aim of the presurgical evaluation is to identify the EZ, ie the minimum amount of brain tissue that should be resected to render the patient seizure-free. At the present time, none of the available investigations allows direct delineation of the EZ. Thus, the identification of the EZ results from the integration of the following information: the sequence of ictal signs and symptoms that defines the symptomatogenic zone, the brain regions that generate interictal electroencephalographic (EEG) epileptiform discharges (so-called irritative zone), the ictal onset zone corresponding to the region of EEG seizure onset, and the epileptogenic lesion disclosed by magnetic resonance imaging (MRI).[23] Two other regions need to be identified to ensure a safe and optimal surgical treatment, ie, eloquent cortex and the functional deficit zone. Finally, several indicators of postoperative outcome need to be gathered to anticipate the chance of successful epilepsy surgery.

Three types of investigations should be distinguished: (i) those considered mandatory for every patient, which include a detailed past history and description of seizures by the patient and his or her relatives, interictal scalp EEG data, and an optimal brain MRI unless contraindicated; (ii) long-term video-EEG monitoring that allows capture of the patient's seizure is also considered a mandatory investigation in the majority of epilepsy surgery centers, but some groups argue that it might be skipped in a minority of patients; and (iii) all other investigations that are either used in selected patients in most epilepsy surgery centers, or in some centers only. Invasive EEG recordings and the Wada test illustrate the former situation, whereas positron-emission tomography (PET), ictal single photon-emission computed tomography (SPECT), and magnetoencephalography (MEG) are examples of the latter.

Mandatory investigations

A detailed interview of the patient and his or her parents, relatives, or friends who have witnessed the seizures remains the cornerstone of the presurgical evaluation. This interview should recapitulate all relevant past history and provide the most detailed description of the patient's seizure. For instance, lateralized and prolonged febrile convulsions are likely to be associated with a temporal lobe EZ contralateral to the side of convulsions, and with an excellent seizure outcome following TLE surgery.[9,24] Conversely a severe herpes virus meningoencephalitis is more likely to result in multifocal or bilateral drug-resistant epilepsy not amenable to successful surgical treatment.[25,26] Family history of neurological and epileptic disorders must also be sought, and may help to identify a specific syndrome, such as autosomal dominant nocturnal frontal lobe epilepsy (NFLE)[27] or TLE,[28] or *forme frustre* of tuberous sclerosis.[29] A detailed assessment of the patient's hand, eye, and foot dominance, together with the description of his or her ictal and postictal language abilities, allows inference regarding the most likely side of seizure onset. Stereotyped auras that can be precisely described by the patient often represent one of the most reliable indicators of the seizure onset zone. This is particularly true for elementary sensory or motor signs pointing to the corresponding primary or secondary cortical areas, but also for rising epigastric sensation, *déjà vu, déjà vécu*, and dreamy state that strongly suggest a temporal lobe seizure onset. However, like any other ictal symptom, auras might only reflect the propagation into the symptomatogenic zone of an epileptic discharge that has originated in a distant silent brain region. It is also essential to assess the presence and frequency of secondary generalization, since the latter supports an extratemporal EZ and predicts a poor outcome following temporal lobe surgery.[6]

A comprehensive cognitive and psychiatric evaluation is likely to provide useful information. Some neuropsychological dysfunctions are associated with specific EZ, such as verbal memory impairment with left TLE.[30] More importantly, the degree of preoperative verbal memory impairment is a strong predictor of postoperative memory decline following surgery in the dominant temporal lobe.[31,32] The lower the preoperative impairment, the greater the risk of postsurgical deterioration. In addition, diffuse neuropsychological deficits may be an indicator of extensive brain disease and therefore a marker of poor outcome following focal resection.[33,34] The prevalence of psychiatric disorders in patients referred to epilepsy surgery might be as much as 80%.[35] Whether these disorders increase the risk of postoperative seizure recurrence remains controversial.[36,37] Likewise, they do not necessarily predict the risk of postoperative psychiatric complications, except maybe for personality disorders.[38-40] Thus, mental disorders do not preclude epilepsy surgery. Nevertheless, their appropriate assessment by a psychiatrist with specific expertise in epilepsy might help to anticipate acute anxiety, delusions, or aggressive behavior during long-term EEG monitoring (in particular following a cluster of seizures favored by the tapering of AEDs during invasive EEG monitoring), and in the immediate postoperative period (in particular following right temporal lobectomy).[41] In addition, such assessment allows better evaluation of the patient's understanding of, and expectations from, the presurgical workup, and whether these are in line with the reality.

Interictal EEGs often demonstrate epileptiform discharges in patients with drug-resistant epilepsy, providing important hints regarding the lateralization and localization of the EZ. However, these abnormalities might be falsely localizing in a minority of cases. In TLE, the presence of unilateral anterior temporal spikes is a strong predictor of postoperative seizure freedom, whereas the lack of epileptiform discharge and bilateral abnormalities are associated with poorer prognosis.[24] Nevertheless, bitemporal spikes, either synchronous or independent from each other, do not preclude successful temporal surgery, provided that they predominate on the side to be resected.[42] Similarly, multifocal and generalized epileptiform discharges are compatible with successful surgery in children presenting with an epileptogenic unilateral brain lesion,[17] as well as in patients with tuberous sclerosis.[43] Specific EEG patterns, characterized by well localized repetitive fast spikes associated with short burst of low-voltage, high-frequency oscillations might help to suspect an underlying MRI-occult focal cortical dysplasia.[44]

An optimal high-resolution MRI is of paramount importance to detect a structural abnormality most likely responsible for the seizure disorder. It is clear that the EZ might often extend outside the MRI-detected borders of such abnormality, and that epilepsy surgery can be successfully performed in patients with a normal MRI.[45-47] However, in the great majority of patients who have been operated on, MRI discloses an epileptogenic

brain lesion that represents the core of the presurgical and surgical strategy. Indeed, other investigations will primarily assess the relationship between seizures and the MRI lesion, the amount of abnormal brain tissue and surrounding cortex included in the EZ, and the possibility of surgically removing part or all of the lesion and associated epileptogenic cortex. This framework is similarly applied to hippocampal sclerosis, malformation of cortical development, scars of various origins, and any space-occupying lesion. The quality of the MRI investigation has a major impact on its sensitivity. Those performed by neuroradiologists with specific expertise in the field of epilepsy surgery have the highest detection rate.[48] Three-dimensional T1-weighted images, as well as T2 and fluid attenuated inversion recovery (FLAIR) sequences, need to be performed using appropriate slice thickness and orientation. In TLE, coronal cuts perpendicular to the long axis of the hippocampus are required to correctly assess the presence of hippocampal atrophy and gliosis. Gradient echo sequences can be useful to detect small cavernous angiomas, whereas gadolinium should be used when a tumor is observed or suspected. Recent reports suggest that the use of 3-Tesla magnets increases the detection rate of subtle epileptogenic lesions, including focal cortical dysplasia.[49]

Long term video-scalp EEG monitoring

In the majority of surgical candidates, video-EEG monitoring plays an essential role in the presurgical evaluation, by providing a detailed description of ictal clinical signs and EEG discharge, as well as prolonged interictal recordings. We have previously commented on the value of ictal semiology and interictal EEG abnormalities. Ictal EEG also provides valuable lateralizing and localizing information with regard to the ictal onset zone.[50,51] However, it might be misleading in patients with a deeply located focus (ie, mesial frontal, parietal, occipital, or insular), by either failing to detect a clearcut epileptic discharge, or by only showing the seizure spread to distant cortical areas.[52,53]
In rare instances, a surgical decision might be taken without a video-EEG recording of seizures. This applies to patients with simple partial seizures that perfectly match with the location of a focal epileptogenic lesion involving the corresponding primary sensory or motor cortex, a situation where the information provided by the video-scalp EEG recording of seizure is unlikely to influence the surgical strategy.

Optional investigations

Three major caveats must be considered when discussing the utility of these presurgical investigations:

1. None of these diagnostic tools has been properly evaluated through RCTs whose primary end point should be their impact on the proportion of patients successfully operated. In 2006, the Health Technological Assessment (HTA) program of the UK National Health Service (NHS) published a comprehensive *"systematic review of the effectiveness and cost-effectiveness of neuroimaging assessments used to visualise the seizure focus in people with refractory epilepsy being considered for surgery."*[54] Their main conclusion was that *"Due to the limitations of the included studies, the results of this review do little to inform clinical practice, with insufficient evidence regarding effectiveness and cost-effectiveness of imaging techniques in the work-up for epilepsy surgery."*
2. There is no consensus regarding the optimal gold standard that should be used for assessing the performance of these presurgical investigations. Invasive EEG recording has been used in some studies, but it faces several limitations, including a variety of techniques (subdural grids versus depths electrodes), limited spatial sampling, investigator dependent placement of electrodes, population bias, and a potential for misdiagnosis. Postoperative seizure freedom is another possible gold standard that also raises a number of issues, such as the time elapsed between surgery and the last follow-up, the postoperative management of AED regimen, the quality of the surgical procedure, and the complex process through which an investigation might interact with the surgical strategy.
3. Last but not least, there is a great heterogeneity in the way presurgical data are analyzed, most notably for functional neuroimaging. Visual analysis is much less reproducible for such data than it is for structural MRI, whereas more objective assessments, using regions of interest (ROIs) or statistical parametric mapping (SPM), are highly sensitive to a number of parameters that largely varied among centers.

Though we fully endorse the conclusions of the NHS R&D HTA program regarding the need of an appropriate assessment of presurgical investigations, we feel that such an effort is unlikely to be developed for the majority of available techniques in the near future. Thus, we still need to primarily rely on our judgment to define the strategy of an optimal presurgical evaluation.

Positron emission tomography (PET)

The most commonly used tracer is ^{18}F-fluorodeoxyglucose (FDG) whose brain accumulation reflects the local cerebral metabolic rate of glucose. Many studies have shown that in the interictal period, decreased glucose metabolism is usually observed within the lobe of seizure onset. Furthermore, comparisons between FDG-PET and invasive EEG data have demonstrated that the hypometabolic areas often overlap with the region of ictal onset.[55-57] However, areas of hypometabolism are often larger than the epileptogenic zone, and might not necessarily predominate over the latter.[58] Whether the extent of hypometabolism outside the temporal lobe represents a risk factor for postoperative seizure recurrence after anterior temporal lobectomy is a matter of debate.[59-61] The above issues account for the lack of consensual practical guidelines regarding the clinical indications of FDG-PET in the presurgical evaluation of patients with drug-resistant epilepsy.[54,62-64] There is, however, some consensus that the lack of detectable interictal hypometabolism in patients contemplating temporal lobe surgery is associated with a poor seizure outcome.[65-67] This finding might be particularly relevant in TLE patients with a normal MRI. Indeed, excellent seizure outcome was reported in that population, provided FDG-PET abnormalities were present.[45] More generally, FDG-PET in patients with a seemingly normal MRI might help to disclose subtle morphological abnormalities, including focal cortical dysplasia. Thus, despite the lack of official recommendation, it seems reasonable to offer FDG-PET, at least to surgical candidates whose MRI is normal.

[^{11}C]Flumazenil (FMZ) PET allows measurement of the apparent density of the γ-aminobutyric acid $(GABA)_A$ receptor allosteric site for benzodiazepine (BZD), which is typically reduced in epileptogenic foci.[68] This abnormality is thought to primarily reflect neuronal loss,[69] but its fluctuation over time observed in patients scanned twice also suggest underlying functional disturbances of the $GABA)_A$ receptor complex.[70,71] FMZ-PET has also been extensively evaluated in patients with drug-resistant partial epilepsy, and has consistently demonstrated more focal abnormalities than FDG-PET.[72] However, the issue as to whether FMZ-PET allows a more precise delineation of the epileptogenic zone than FDG-PET remains a matter of debate.[55,73] In particular, in patients with a normal MRI, FMZ-PET might suffer a higher rate of negative or falsely localizing findings than FDG-PET.[55,70,71,74] Finally, in patients with TLE and MRI signs of hippocampal sclerosis, FMZ-PET might disclose periventricular white matter increased binding of [^{11}C]Flumazenil, thought to reflect microscopic heterotopia, which were found associated with poor postoperative seizure outcome.[75] This finding, if replicated, could support the clinical utility of FMZ-PET as a prognostic tool in TLE patients contemplating surgery.

In patient with tuberous sclerosis and multiple tubers, PET using [^{11}C]alpha-methyl-L-tryptophan (AMT) appears to be the only interictal imaging investigation that can specifically identify which of the multiple tubers is responsible for the seizure disorder, by showing an increased AMT uptake within that tuber.[76] However, this pattern is only observed in half of the patients.[77-79]

More recently, several studies have used different markers of $5\text{-}HT_{1A}$ receptors in patients with drug-resistant TLE, including [^{11}C]WAY100635, [^{18}F]FC-WAY, and [^{18}F]MPPF, and consistently showed major decreased of binding potential within the epileptogenic temporal lobe.[80-83] Whether these PET investigations will prove more clinically useful than, or complementary to, FDG and FMZ-PET remain to be elucidated.

Ictal SPECT

Ictal SPECT remains the only imaging method that can routinely capture clinically overt seizures, regardless of the patient ictal movements. The most typical pattern observed on ictal SPECT images is a focal area of hyperperfusion, thought to reflect the ictal discharge, with surrounding hypoperfusion. The delineation of these abnormalities is optimized by subtracting interictal from ictal SPECT images from the same patient, and coregistering the resulting data on his or her MRI (subtraction ictal SPECT coregistered with MRI, SISCOM).[84] Recent attempts to detect significant ictal hyperperfusion by comparing ictal SPECT to a database of interictal SPECT performed in normal subjects also proved promising.[85] The earlier the timing of injection after seizure onset, the more sensitive and reliable the results of ictal SPECT.

Like FDG-PET abnormalities, ictal hyperperfusion is likely to reflect the impact of the ictal discharge in regions of seizure onset and propagation.[86] However, it is assumed that the epileptic discharge is more sustained within the epileptogenic zone, and that this should translate into greater hyperperfusion in this region than in areas of seizure propagation. This is only partly con-

firmed by empirical evidence, derived from the comparison of ictal SPECT data with that of other investigations, including intracranial EEG recordings and surgical results. Indeed, a few papers have looked at the correspondence between the ictal onset zone as defined by invasive EEG investigation, and ictal hyperperfusion, and reported variable degrees of concordance or overlap between the two.[87] According to these results, the role of ictal SPECT in surgical candidates who would otherwise require intracranial EEG recordings seems rather to help optimize the placement of the intracranial electrodes than to replace this invasive investigation.[88,89] For instance, in a recent series of 26 patients who benefited from SISCOM and subsequent invasive EEG, the former was found to modify the placement of intracranial electrodes in 58% of cases.[88]

Like FDG-PET, ictal SPECT might also help to detect subtle focal cortical dysplasia not readily detectable on MRI,[90] and to predict the chance of postoperative seizure freedom.[91,92] In particular, in patients with a normal MRI or an extensive malformation of cortical development, the more complete the resection of the brain region showing ictal hyperperfusion, the better the surgical outcome.[91,92] However, a complete resection of the SISCOM focus does not seem to be mandatory to achieve complete seizure freedom in patients with focal cortical dysplasia.[90]

As detailed above, the potential clinical utility of ictal SPECT appears to primarily lie in patients with a normal MRI as well as in the prediction of surgical outcome, two issues that have also proved to be the most relevant clinical indications for FDG-PET. The two investigations have been directly compared with each other in several studies.[56,57,93-96] They appear to provide comparable localizing information in a majority of cases, but can also point at strikingly different regions in a minority of patients.[56,57] Ictal SPECT might be more sensitive than FDG-PET in epileptogenic zones involving the parietal and occipital lobes,[94] and more appropriate for evaluating the epileptogenicity of large malformation of cortical development.[91] Conversely, in one of the largest studies of patients with a normal MRI, FDG-PET was found to be superior to ictal SPECT for predicting postoperative seizure outcome.[57] Furthermore, FDG-PET remains more readily available than ictal SPECT in most epilepsy surgery centers. At the present time, there is no consensus regarding the clinical situations where these two investigations should be combined.

1H magnetic resonance spectroscopy

1H magnetic resonance spectroscopy (MRS) has been assessed much less extensively than PET and SPECT, and primarily in patients with TLE. This technique suffers two main drawbacks, a relatively poor spatial resolution (though the later has increased from 8 cm^3 voxels in the earlier studies to 1 cm^3 voxels at present), and a limited spatial sampling of the brain that requires an a priori hypothesis regarding the localization of the epileptogenic zone. In TLE, 1H MRS typically demonstrates reduced N-acetyl aspartate (NAA)/choline and creatine ratio in the epileptogenic temporal lobe, often associated with less marked contralateral abnormalities.[97-99] This finding was also observed in patients with MRI-negative TLE.[97,99-101] The few studies performed in extratemporal epilepsies have also reported reduced NAA/choline and creatine ratio in the epileptogenic zone, as well as in the irritative zone.[102-104]

According to all above findings, and the technical limitations of 1H MRS, it appears that the primary clinical utility of this investigation would be the prediction of postoperative seizure outcome in TLE patients, especially those with a normal MRI or bilateral hippocampal atrophy.[100,105-107] However, it still needs to be demonstrated whether H1 MRS is an independent predictor of surgical outcome, taking into account all other relevant clinical and imaging data.

Magnetoencephalography

The technology of multichannel magnetoencephalography (MEG) has considerably improved over the last 10 years, with a dramatic increase in the number of recording channels, up to 300 sensors,[108] and the development of more efficient data analysis using magnetic source imaging (MSI) and spatial filtering by means of synthetic aperture magnetometry (SAM).[109] This development necessitates revisiting the clinical utility of MEG in the presurgical evaluation of patients with epilepsy,[110] though the main limitation of MEG remains its lack of availability in the majority of epilepsy surgery centers.

MEG primarily detects interictal epileptiform discharges, though in rare instances ictal recordings could be performed.[111] It was found to be more sensitive than scalp EEG, in particular for the detection of neocortical spikes, but also more potent for delineating the maximal source of interictal epileptiform discharges.[112] MSI was com-

pared with intracranial EEG recordings in 49 patients and demonstrated a predictive positive value for seizure localization of 82%.[113]
Like FDG-PET, ictal SPECT, and 1H MRS, MSI might also help to disclose a brain lesion not readily detectable on MRI and to better predict postoperative seizure outcome.[110,114,115] The only study that has compared MEG and FDG-PET demonstrated congruent findings in the majority of patients.[116] MEG appears to have a more specific impact than the above investigations on the localization of epileptogenic tuber,[117] and of spiking cortex underlying Landau-Kleffner syndrome.[118] In addition, MEG does not involve the inconvenience of injecting a radioactive compound such as for PET and SPECT, nor the distressing effect of MRI observed in some patients, particularly children.
Though future studies are needed to thoroughly assess the clinical utility of MEG compared with, or in association with, other presurgical investigations, it seems reasonable for centers that have access to this very safe procedure to use it without much restriction.

Functional MRI

Functional MRI (fMRI) has proved reliable for mapping eloquent areas in patients contemplating epilepsy surgery. It can be used for localizing the sensorimotor cortex or language areas when these functional brain regions are at risk to be included in the EZ. However, if a surgical resection is planned in the vicinity of fMRI-activated brain regions, intraoperative cortical mapping remains mandatory to more precisely assess the extent of these eloquent areas. Several studies have demonstrated that fMRI was also effective and reliable for the lateralization of language dominance in patients with epilepsy,[119,120] including one large series of 100 patients where it was compared with the Wada test.[121]
In the near future, fMRI may also replace the Wada test for the assessment of memory capacities within each temporal lobe.[122-125] One study that directly compared the two investigations concluded that fMRI more precisely anticipate the postoperative memory decline than the Wada test.[122]
fMRI might also be used in combination with scalp EEG to detect focal BOLD activation induced by interictal epileptiform discharges, subclinical seizures, or paucisymptomatic ictal events.[126-128] Sophisticated data analysis, such as temporal cluster analysis, might also demonstrate focal BOLD signal abnormalities supposedly reflecting interictal epileptiform activity, without necessitating concomitant EEG recording.[129] However, the clinical utility of these developing techniques remains to be evaluated.

Intracarotid amytal test or Wada test

The Wada test has been extensively used in the past for assessing the side of language dominance and the risk of memory decline following temporal lobe surgery.[130] As previously discussed, its utility for lateralizing language areas has now been challenged by fMRI. For memory assessment, where fMRI remains to be fully validated, the Wada test appears to be primarily useful in patients with left (dominant) TLE.[131]

Intracranial EEG

Intracranial EEG recording remains a mandatory investigation in a significant proportion of epilepsy surgery candidates, in order to ensure the delineation of the EZ. Though the precise criteria used to proceed to such invasive recordings largely vary between centers, some general recommendations can be made regarding this issue: (i) intracranial EEG recording should tackle a specific hypothesis regarding the localization of the EZ, and not be performed as a "fishing expedition"; (ii) appropriate candidates might include patients with a normal MRI, patients with symptomatic extra-temporal lobe epilepsy where a simple lesionectomy appears unlikely to control seizures, and patients with a temporal lobe MRI abnormality associated with atypical electroclinical features for TLE, suggesting the possibility of temporal plus epilepsy.[53,132] Two main types of invasive recordings are available: subdural grids that are used in the great majority of epilepsy surgery centers worldwide, and depth-electrodes, including stereoelectroencephalography (SEEG), that are primarily used in French and Italian centers. Both techniques have specific advantages and drawbacks, and suffer from limited spatial sampling. Subdural grids can provide an accurate delineation of EZ located on the cortical surface of the brain, whereas SEEG appears more appropriate for investigating deeply located EZ, such as in the insula, the mesial aspects of the frontal, temporal, parietal, and occipital lobe, or the bottom of deep sulci.[52,132-136] In any case, the placement of subdural or depth electrodes is individualized according to all available presurgical data. Complications of these invasive procedures are usually

minor and occur in only 1% to 2% of cases.[137] A large number of relevant information can be provided by intracranial EEG recordings, including interictal slow waves, spikes, and bursts of high frequency oscillations, ictal discharges, and responses to various types of electrical cerebral stimulation. It was recently shown that abnormal high frequency oscillations, including ripples and fast ripples, either occurring at seizure onset or during interictal bursts, were the most reliable marker of the EZ.[138-141] High- and low-frequency electrical stimulation of the suspected EZ can be used to reproduce the patient's ictal signs and EEG discharges, and to test eloquent cortex.

Conclusions

Thanks to the advances of many investigations, an increasing number of patients with drug-resistant epilepsy can benefit from a conclusive presurgical evaluation that will hopefully lead to a successful surgical treatment. Nevertheless, important progress still needs to be achieved in order to assess the performance and specific impact of these various investigations more rigorously. Large multicenter randomized controlled trials should be the method of choice whenever possible. Such trials are likely to promote more homogeneous presurgical strategy among centers and countries. In turn, harmonization of practice should result in increasing the yield of successful epilepsy surgery. Dissemination of current knowledge regarding the eligibility criteria for entering a presurgical evaluation and the success rate of epilepsy surgery represents another major challenge in the field. This should allow more patients with refractory seizures to benefit from a timely and effective surgical cure of their devastating disease. ❑

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Cirugía en epilepsia: criterios de elegibilidad y evaluación prequirúrgica

La cirugía en la epilepsia se ha beneficiado en los últimos 20 años de importantes avances, gracias al desarrollo de las neuroimágenes y del monitoreo video-electroencefalográfico de larga duración (EEG). Sin embargo, se mantiene la situación que sólo una pequeña minoría de potenciales candidatos a la cirugía de la epilepsia tendrá acceso a una exhaustiva evaluación prequirúrgica. Además, este subgrupo de pacientes es operado después de un promedio de 20 a 25 años de duración de la epilepsia. Entre las diversas razones que impiden que muchos pacientes se beneficien de una oportuna evaluación prequirúrgica es necesario enfatizar el papel de la información imprecisa en relación con los criterios de elegibilidad y la falta de prácticas estandarizadas. Esta revisión se orienta a proveer una discusión en profundidad de las visiones actuales relacionadas con la definición de candidatos quirúrgicos y el papel de numerosas investigaciones utilizadas en la evaluación prequirúrgica de pacientes con epilepsia resistente a fármacos. Los criterios de elegibilidad requeridos para incluirse en una evaluación prequirúrgica en 2008 deben ser relativamente flexibles, siempre que el paciente sufra de crisis convulsivas incapacitantes no relacionadas con un síndrome epiléptico generalizado idiopático, a pesar de un apropiado tratamiento con fármacos antiepilépticos. Sin embargo, la decisión de llevar a cabo o no una evaluación prequirúrgica debe ser individualizada y tomar en cuenta la probabilidad de satisfacer las expectativas del paciente en términos de su evolución. Estas expectativas necesitan ser balanceadas con la aparente gravedad de la condición epiléptica, la posibilidad de conseguir un tratamiento quirúrgico exitoso y el riesgo de un deterioro neurológico, cognitivo y psiquiátrico postoperatorio. Se revisarán los papeles y características específicas de los tres principales tipos de investigaciones prequirúrgicas.

Chirurgie de l'épilepsie : critères d'éligibilité et évaluation préchirurgicale

Des progrès considérables ont été réalisés lors de ces 20 dernières années dans le domaine de la chirurgie de l'épilepsie, liés principalement aux développements de la neuro-imagerie et du monitorage à long terme vidéo-électro-encéphalographique. Cependant, seule une faible minorité des candidats potentiels à un traitement chirurgical de leur épilepsie ont accès à un tel bilan pré-chirurgical. De plus, ceux qui en bénéficient sont opérés en moyenne après 20 à 25 années d'évolution de leur maladie. Une profonde méconnaissance des critères d'éligibilité à la chirurgie de l'épilepsie, ainsi qu'une standardisation insuffisante de ce type de traitement, concourent à cette situation défavorable. Cette mise au point approfondie vise à présenter l'état actuel de nos connaissances sur le profil des candidats à une chirurgie de l'épilepsie, et sur les moyens à mettre en œuvre pour évaluer avant l'intervention les patients résistants au traitement antiépileptique. En 2008, les critères d'éligibilité en vue de bénéficier d'un bilan préchirurgical doivent être relativement larges, essentiellement fondés sur la présence de crises d'épilepsie invalidantes et réfractaires à un traitement médical bien conduit, sans rapport avec un syndrome d'épilepsie généralisée idiopathique. Cependant, la décision de réaliser un tel bilan reste individuelle, et nécessite de prendre en compte les chances réelles d'aboutir à un traitement chirurgical dont le résultat répondra aux attentes du patient. Il s'agit notamment de prendre en compte la sévérité apparente de la maladie, les chances de guérison des crises par la chirurgie, mais aussi le risque de complications neurologiques, cognitives, ou psychiatriques postopératoires. L'intérêt clinique et la place de chacune des principales explorations préchirurgicales seront par ailleurs discutés.

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