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Presurgical evaluation and surgical treatment of medically refractory epilepsy

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Abstract Thanks to today's modern imaging examination techniques and especially to the common use of intracranial electrodes for localizing seizure foci, more and more patients with partial epilepsy can be treated microsurgically. The results of such neurosurgical therapies are very good, particularly in mesial temporal lobe epilepsy. In recent years, good results (60–70% seizure freedom) have also been achieved in extratemporal epilepsy surgery, so that such procedures can now be recommended for carefully selected patients. In this review, presurgical evaluations and the different surgical approaches are presented.

Keywords Epilepsy · Epilepsy surgery · Invasive electroencephalography · Magnetic resonance imaging · Presurgical evaluation · Seizure outcome

Introduction

Epilepsy is one of the more common neurological diseases, with a prevalence of 0.5–1.0% and estimated lifetime cumulative incidence of 3% [79, 81]. It may arise from a constitutional predisposition or as a consequence of acquired cerebral pathology. Specific causes for epilepsy differ with geographic areas, but idiopathic/cryptogenic epilepsies are the most frequent type, accounting for two thirds of all new cases [79, 81]. In patients with identified etiology for epilepsy, cerebrovascular disease is the most common cause (accounting for 10.9% of new cases), followed by congenital diseases

(8%), trauma (5.5%), neoplasms (4.1%), degenerative disorders (3.5%), and infections (2.5%) [81].

Approximately 40% of the patients suffer from generalized seizures and 60% from focal (partial) seizures [78]. About 55% of focal epilepsies in which seizures originate from a circumscribed cerebral region are temporal lobe epilepsies. Epilepsies of the frontal, parietal, or occipital lobe make up the remaining 45%. This heterogeneity in the causes and clinical syndromes of epilepsy is also reflected in the different therapeutic approaches, which mainly consist of antiepileptic medication and, in some cases, epilepsy surgery.

Complete seizure control and improvement of quality of life are the main goals of any treatment. Antiepileptic drugs are usually given as the first therapeutic step. However, fewer than 33% of all patients achieve full control of seizures for 1 year on monotherapy, and only 10–20% of the failures achieve full control of seizures with two-drug therapy [128, 129, 178, 194, 198, 206, 240].

Interestingly, the percentage of drug-resistant epilepsies has not diminished significantly, in spite of the new antiepileptic drugs [17, 115, 131, 174]. Overall, about 30–40% of all patients with epilepsy have medically intractable seizures, and 50% of these are candidates for epilepsy surgery [2, 20, 44, 53, 80, 196]. For the United States, it has been estimated that there are more than 100,000 candidates for surgical treatment, with 5,000–10,000 added annually [31, 32, 53]. Despite this large number of potential surgical candidates, only 2,000 surgical procedures were performed per year in the United States [53, 80]. This discrepancy in need and utilization may be explained by:

1. Ignorance among primary care physicians of the recent advances in safety and efficacy of surgical epilepsy treatment
2. The fact that some patients prefer to tolerate seizures and side effects rather than undergo surgery
3. The lack of funding by third-parties for the expensive presurgical workup and surgical treatment, even

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though several studies have shown their cost effectiveness [18, 56]

In the last decade, however, epilepsy surgery has gained acceptance, and a large number of patients have been operated on throughout the world. This new interest can be explained by the advances in presurgical evaluation and improved surgical techniques. Modern presurgical workup includes noninvasive and invasive telemetric long-term EEG monitoring, quantitative magnetic resonance imaging (MRI), functional MRI, positron emission tomography (PET), single photon emission tomography (SPECT), MR spectroscopy (MRS), and magnetoencephalography (MEG).

New surgical techniques have made epilepsy surgery safer and more effective. For instance, the introduction of microneurosurgery has allowed more selective operations such as selective amygdalohippocampectomy [145, 255]. Furthermore, palliative surgical procedures such as multiple subpial transection and the formerly more common partial callosotomy have witnessed renewed interest [130, 138, 140, 179, 180, 209, 281]. Some centers have also evaluated new approaches such as radiosurgery for the treatment of partial epilepsy [170, 171, 172, 173, 227].

The extent to which today's possibilities of epilepsy surgery have changed the neurologist's daily routine can be illustrated best with the example of so-called mesial temporal lobe epilepsy, the most common form of focal epilepsy. In this type, seizures are generated in the amygdala and the hippocampal formation. Mesial temporal lobe epilepsy was long reputed to be incurable, and patients could only be abandoned to their fate. However, the currently available interventions, anterior 2/3 temporal lobectomy or the less crude selective amygdalohippocampectomy (specific resection of the two mesial temporal structures causing the seizures), lead to postsurgical freedom from seizures in about 80% of patients [54, 145, 200, 212, 255, 258]. These good operative results, reached over several decades, now make it clear why unsuccessful drug therapy for medically refractory mesial temporal lobe epilepsy should no longer be continued indefinitely. Rather, such patients should be operated on as soon as possible.

Whereas the treatment of mesial temporal lobe epilepsy has been significantly simplified by surgery, drug-resistant extratemporal epilepsies still constitute a major challenge to epileptologists and neurosurgeons. Until about 10 years ago, the results of major epilepsy centers with this category of patients were rather disappointing, and quite frequently only 40–50% of the patients showed postsurgical seizure-free outcomes; but also with extratemporal epilepsies, the development of imaging procedures has simplified precise seizure localization. Furthermore, improved neurosurgical techniques have increasingly led to very good operative results, so that surgical interventions must also be considered as a therapeutic option for drug-resistant extratemporal epilepsies.

Abnormal brain areas involved in interictal and ictal activity

When epilepsy surgery is considered, presurgical workup must define the different brain areas that either generate seizures or are involved in interictal and ictal epileptiform activity. Lüders proposed a theoretical concept that distinguishes six brain areas (Table 1) [121, 122, 184]. The identification of these areas allows neurosurgeons and neurologists not only to tailor the resection but also predict postoperative deficits to a certain extent. Therefore, it becomes clear that presurgical evaluation includes several different types of diagnostic studies.

Current indications for epilepsy surgery

Before an indication for the surgical treatment of epilepsy can be established, the tentative diagnosis of epilepsy must be verified. This may sound banal but, as the diagnosis sets the course for possible further diagnostic procedures, it has an important role. In epileptology, as elsewhere in clinical medicine, history is also one of the most important diagnostic tools, because exact observation allows the differentiation of epileptic seizures from nonepileptic ones, while an accurate history usually

Table 1 Definition of abnormal brain areas (modified from [121, 122, 184])

Irritative zone	Area of cortex that produces interictal spikes	Electrophysiological (invasive and noninvasive)
Ictal onset zone	Area of cortex from which seizures originates (incl. areas of early propagation, under certain circumstances)	Electrophysiological (invasive and noninvasive)
Epileptogenic lesion	Structural brain abnormality that is the ultimate cause of the seizures	Structural imaging and tissue pathology
Symptomatogenic zone	Portion of the brain that produces the initial clinical symptomatology	Behavioral observation and patient report
Functional deficit zone	Cortical area with functional abnormalities	Neurologic examination, neuropsychological testing, EEG, PET, SPECT
Epileptogenic zone	The area of brain that is necessary and sufficient for initiating seizures and whose removal or disconnection is necessary for abolition of seizures	Theoretical concept

Table 2 Typical seizure characteristics [12, 25, 55, 96, 186, 189, 190, 201, 202, 260, 263, 268; 269, 270]

Frontal lobe seizures	<p>Brief seizures often in clusters, predominantly nocturnal</p> <p>Sudden beginning and ending with minimal postictal confusion</p> <p>Typical features: focal clonic motor activity (march following the motor homunculus), complex and bizarre (gestural) automatisms (therefore often misdiagnosed as hysteric seizures), forced vocalization (“mumbling”, “shouting”), kicking, stepping, rocking, or cycling movements</p> <p>Rapid secondary generalization, often drop attacks and status epilepticus, urinary incontinence common</p> <p>Based on seizure origin six subtypes of frontal lobe seizures are distinguished: SMA/mesial, orbitofrontal, frontal convexity, frontopolar, cingulate, opercular (also considered as type of insular seizures)</p> <p>Supplementary motor area seizures: contralateral lateral abduction and external rotation of the arm at the shoulder, forceful deviation of the head (“fencing posture”), focal tonic motor signs, speech arrest</p> <p>Orbitofrontal seizures: abrupt onset of bizarre attacks, motor and gestural automatisms, olfactory hallucinations and illusions, autonomic signs, screaming, yelling, coughing, laughing, kicking, stepping, rocking, or cycling movements, sexual automatisms</p> <p>Frontal convexity (dorsolateral frontal lobe) seizures: tonic or, less common, clonic signs, (contralateral or ipsilateral) head and eye deviation, rocking</p> <p>Frontopolar seizures: head and eye deviation, unilateral facial contractions, due to minor motor signs if seizures remain frontopolar also called “pseudoabsences”</p> <p>Anterior cingulate gyrus seizures: poorly defined, changes in mood and affect, vegetative signs, gestural automatisms</p> <p>Frontal opercular seizures: mastication, salivation, laryngeal sensations, swallowing, epigastric sensation with fear and/or vegetative phenomena, speech arrest and aphasia if seizures confined to the dominant frontal lobe</p>
Temporal lobe seizures	<p>In up to 80% auras (e.g. Rising epigastric discomfort, déjà vu, micropsia/macropsia, fear, etc.)</p> <p>Often alteration of consciousness, loss of consciousness if both temporal lobes are involved</p> <p>Often secondary generalization</p> <p>Mesial temporal lobe epilepsy (MTLE) most common type of focal epilepsy</p> <p>Typical features: rising epigastric discomfort, olfactory and/or gustatory hallucinations, Nausea, autonomic signs such as pallor, belching, borborygmi, flushing and/or fullness of the face, arrest of respiration, pupillary dilatation, fear, panic, déjà vu, déjà entendu, déjà vécu, oro-alimentary automatisms</p> <p>Neocortical lateral temporal lobe epilepsy (NLTLE)</p> <p>Typical features: auras of auditory hallucinations or illusions or dreamy state, visual perceptual misperceptions, disturbances in language if seizures confined to the dominant temporal lobe, vertiginous symptoms</p>
Parietal lobe seizures	<p>Ictal discharges, clinically often silent</p> <p>Typical features: contralateral paresthetic (numbness and tingling, “pins and needles”), dysesthetic, and, rarely, painful seizures</p> <p>Rare features: apraxias, gustatory hallucinations (parietal operculum), spatial disorientation, feeling of body rotation (“crise giratoires”), autopagnosia (e.g. Alien hand), asomatognosia, sexual automatism/sensation, disturbances in language if seizures confined to the dominant parietal lobe, “psychoparetic” seizures with déjà vu or fear followed by impairment of consciousness and motor arrest</p> <p>Unspecific features: nausea, vertigo</p> <p>Signs of extraparietal propagation: motor arrest, gestural or oral automatisms, asymmetric posturing, visual hallucinations or amaurosis</p>
Occipital lobe seizures	<p>Elementary visual hallucinations (e.g., micro-/macropsia, often lateralized), ictal amaurosis (bilateral, hemianopsia, blackout or whiteout)</p> <p>Sensation of eye movement or pulling without detectable motion, eyelid flutter, rapid forced blinking</p> <p>Tonic or clonic eye movement (oculoclonic status epilepticus)</p> <p>Signs for extraoccipital propagation: focal somatosensory and motor features, asymmetric posturing, complex visual hallucinations, gestural and oral automatisms</p>

provides important clues to seizure origin. The typical seizure characteristics of partial epilepsies are summarized in Table 2 [12, 25, 55, 96, 186, 188, 189, 190, 201, 202, 260, 263, 268, 269, 270].

When the tentative diagnosis of partial epilepsy has been made on the basis of history and surgical treatment is considered because of drug-resistant seizures, the next step is to evaluate the patients as candidates for epilepsy surgery according to the following criteria set by Walker [249]:

1. Progressive neurological disease (e.g., malignant brain tumor, cerebral vasculitis, multiple sclerosis, etc.) should be ruled out. Although patients with malignant tumors can also have epileptic seizures, operations relating to this cannot be considered epilepsy surgery

(so-called epilepsy surgery *sensu strictu*), because primarily they do not represent treatment of epilepsy but rather of malignant tumors.

2. The resistance to drug treatment has to be ascertained. Here it is particularly important to make sure that the formerly used antiepileptic drugs have been carefully administered up to the limit of “subjective intoxication.” This means not only that antiepileptic drugs should be given up to the limit within the therapeutic range but that individual differences in metabolism be considered and the drug be given to just below the blood level at which side effects set in (which may be far above the maximum therapeutic level). Furthermore, apart from at least two monotherapies, polytherapies also should have been tried.

3. The duration of the disease has to be at least 1–2 years. However, exceptions are allowed in this respect (particularly with epilepsies due to structural lesions or with early-diagnosed mesial temporal lobe epilepsy).
4. Patients have to be handicapped by the seizures, although this may of course differ significantly from individual to individual. Generally, however, the indication for surgery should be established rather cautiously when the seizures consist only of sensory phenomena without alteration of consciousness, even if they are frequent.
5. The patients should be motivated for the presurgical workup and operation and aware, above all, that they must also take antiepileptic drugs postsurgically.
6. An IQ below 70 strongly suggests diffuse brain disease, in which case the prospects of success of an epilepsy surgery intervention are poor and the surgical indication should be established with caution.
7. Psychiatric diseases are also a contraindication to epilepsy surgery.

Stages of presurgical evaluation

If there are no contraindications to operative intervention on the basis of the aforementioned criteria, the patients normally need further evaluation. This presurgical workup of candidates for epilepsy surgery is comprised of noninvasive (phase I) and invasive (phase II) evaluation. Phase I consists of a detailed history including review of past treatment, neurological exam, neuropsychological testing, psychiatric and psychosocial evaluation, interictal

Table 3 Evaluation for epilepsy surgery (modified from [40])

Phase 1: noninvasive

1. Review of past treatment (AED dosages, trough levels, seizure diaries) and detailed history
2. Medical and neurological examination
3. Neuropsychological testing
4. Psychiatric evaluation
5. Visual field testing (in particular in temporal and occipital lobe surgery)
6. interictal EEG recording (and review of previous EEG's)
7. MRI (with T2-weighted coronal views)
8. Ictal video EEG recordings
9. Interictal PET
10. SPECT (ictal studies)

Phase 2: invasive

1. Bilateral carotid angiogram and intraarterial Amytal test (global and superselective Wada tests)
2. Depth, subdural, and/or epidural electrodes with video-EEG monitoring of interictal and ictal activity
3. Functional mapping with subdural electrodes

Phase 3: intraoperative

1. Electrographic activity of interictal activity
 2. Functional mapping, awake (language, motor, and sensory areas) or asleep (motor [direct stimulation] and somatosensory [evoked potentials])
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and ictal EEG recording (including video EEG monitoring), MEG, structural CT and MRI, MRS, fMRI, SPECT, and PET.

This first phase of presurgical evaluation screens patients considered for surgery. If the epileptogenic focus (zone) can be identified during phase I, the recommendation may be made to proceed directly to epilepsy surgery. In some patients, however, phase I cannot accurately localize the epileptogenic zone, and an additional invasive evaluation (phase II) becomes mandatory. This includes video EEG recording by means of invasive depth, subdural, and/or epidural electrodes and, if necessary, further neuropsychological control with intra-arterial amobarbital tests. At the end of phase II, a final decision can be made whether a patient suffers from a surgically remediable epilepsy syndrome and thus whether surgery with or without intraoperative EEG monitoring (phase III) can be performed (Table 3) [40].

Noninvasive evaluations (phase I)

Scalp electroencephalogram

Scalp (surface) EEG in the waking and sleeping states with simultaneous video monitoring of seizures is one of the more important evaluations in phase I. Video EEG monitoring allows adequate observation not only of seizures but also of the simultaneously recorded EEGs, which enables conclusions to be drawn on the origin of the seizures (lateralization and localization).

Several studies have shown that the repeated incidence of interictal epileptiform potentials in the same cerebral region in multiple EEGs correlates very well with the origin of ictal discharges [5, 213]. Thus, interictal epileptiform discharges may be recorded in 50% of patients during routine awake EEG [103, 157, 163, 164, 197, 252]. In temporal lobe epilepsy, the diagnostic accuracy even increases up to 90% by recording a sleep EEG [29, 197, 252].

In mesial temporal lobe epilepsy, characteristically epileptiform potentials are found in basal areas of the frontal and temporal lobes [260], while in neocortical temporal lobe epilepsy the correlation with these potentials is of varying strength. In temporal lobe epilepsy, ictal surface EEG classically reveals rhythmic sinusoidal theta activity of high amplitude and low frequency [256].

While interictal and ictal surface EEG is very helpful in mesial temporal lobe epilepsy in terms of localization and lateralization of seizure origin, its value in extratemporal epilepsies is highly variable. In frontal lobe epilepsy, interictal and ictal surface EEG often reveals unspecific changes or is completely silent, i.e., abnormal EEG patterns can be observed in only about 10% of the patients [96, 163, 270]. The fact that, in frontal lobe epilepsy with its partially bizarre motor signs, EEG is often not very helpful makes the diagnosis even more difficult and explains frequent misdiagnoses of “hysteric,” “nonepileptic,” or “psychogenic” seizures.

In contrast to frontal lobe epilepsy, interictal as well as ictal epileptiform potentials are frequently observed in epilepsies of the occipital and parietal lobes [11, 202]. Thus parietal epileptiform potentials are found in approximately 65% of patients with parietal lobe epilepsy and occipital potentials in 79–97% of patients with occipital lobe epilepsy. At the same time, only 10% and 14% of patients with parietal and occipital lobe epilepsy, respectively, have normal EEGs [11, 202].

Magnetoencephalography

The basic concept underlying MEG is the measurement of extracranial magnetic fields generated by the electric activity of cortical pyramidal cells [3, 48, 136, 181, 193]. Unlike EEG, MEG is reference-free, as it measures magnetic fields rather than differences in potential.

Numerous studies of MEG in medically intractable epilepsy have shown that it can detect interictal and ictal epileptiform activity [3, 4, 49, 106, 182, 226, 229]. Many studies compared localization by MEG with “standard” localization of the epileptogenic zone as determined by scalp and invasive EEG as well as MRI [50, 106, 207]. Smith et al. performed MEG in 50 patients being evaluated for possible surgery [207]. Of them, 56% had complete agreement between MEG and standard localizations, partial agreement in 12%, no agreement in 10%, lack of spikes in MEG in 16%, and inadequate data in 6% [207]. In this study, MEG was more effective localizing epileptogenic zones involving the cerebral convexity rather than in the deep structures. Other studies led to similar findings, in particular for extratemporal epilepsies [104, 106, 134]. Thus, MEG has been shown to be effective for detecting interictal and ictal epileptiform discharges.

The primary clinical use of MEG includes neocortical epilepsies, cases with normal MRI, and patients with large MRI abnormalities. In these groups, MEG can eliminate the need for invasive EEG monitoring and thereby reduce costs and morbidity. However, since MEG is rather expensive and insurance companies are reluctant to cover the costs, its use in localizing the foci of epileptic seizures is mainly limited to scientific issues.

Structural imaging

The evaluation of patients with epilepsy has been revolutionized by the advent of MRI. It provides the best anatomic detail of any imaging modality and is the most sensitive tool for demonstrating large structural lesions. Because of its superior sensitivity and specificity compared with CT, MRI is the preferred imaging technique in the presurgical workup of patients with medically refractory epilepsy [221].

Usually, high-resolution MRI is performed according to a special epilepsy protocol [9, 22, 34]. In the last decade, this technique has led to the recognition of

smaller, even tiny epileptogenic lesions. Thus, in addition to the tumors and vascular malformations that are most commonly diagnosed today (e.g., cavernous and arteriovenous malformations), very small abnormalities due to migration disorders (cortical dysplasia, polymicrogyria, hamartoma, etc.) can be detected. Apart from these structural abnormalities, MRI in patients with mesial temporal lobe epilepsy often reveals mesial temporal sclerosis, which is characterized by both hippocampal atrophy seen on T1-weighted images and increased hippocampal signal intensity seen on T2-weighted spin-echo images [8, 58, 92, 95, 113, 127, 242]. Although mesial temporal sclerosis can usually be diagnosed by visual inspection of the MRI, modern MRI-based quantitative volume measurement of the hippocampal formation has further improved its sensitivity of detection [23, 90, 114].

In 30–40% of patients with extratemporal epilepsies, epileptogenic tumors are found (ganglioglioma, low-grade astrocytoma, oligodendroglioma, etc.) [27]. Cortical migration disorders are found with the same frequency [27]. Rare structural lesions include Sturge-Weber syndrome, postnatal injuries (porencephalic cysts), scars, etc. Such intracerebral lesions nearly always match with the epileptogenic zones, and patients—provided the further results of noninvasive studies can be explained by the lesion—can be directly passed on to the neurosurgeon [37, 105, 231]. However, in approximately 20% of patients, the most modern MR techniques fail to detect any lesions. Although these surgical candidates are among the most difficult patients to treat, it has been found that epilepsy surgery may yield good seizure outcome in these cases as well [205].

New MRI techniques such as fluid attenuated inversion recovery (FLAIR) sequence and diffusion and perfusion MRI may further help to localize seizure origin [162]. The FLAIR MRI produces images in which parenchymal lesions have a high signal and CSF has a low signal [162]. Thus, FLAIR imaging improved the identification of hippocampal sclerosis and lesions but not of heterotopias [7, 265]. Diffusion-weighted imaging was initially implemented for the identification of acute cerebral infarcts but has also been reported to be sensitive enough for the detection of epileptogenic foci [42, 111, 266]. Though diffusion and perfusion MRI have been found to be very sensitive, their use in presurgical workup still has to be tested.

Functional magnetic resonance imaging

More recent applications of the magnetic resonance technique include fMRI and MRS [152, 191, 192]. The former provides high-resolution, noninvasive measurements of neural activity by means of a signal dependent on the blood oxygen level [63, 64, 87, 93, 239, 250]. Thus, fMRI can supply the neurosurgeon with information about cortical areas that must be spared in the planned resection and, if they are not to be spared, about

the neurological deficits to be expected postoperatively. Even though some of the initial data are very encouraging, at present fMRI has not yet taken over the role of functional mapping with intracranial electrodes in presurgical evaluation for epilepsy surgery. Triggering by EEG may increase the use of this new technique [107, 230, 250].

Magnetic resonance spectroscopy

The only noninvasive technique capable of measuring chemicals within the body, MRS measures chemical changes in the examined cerebral areas by application of the principle that every chemically distinct nucleus in a compound resonates at a slightly different frequency [33, 191]. In patients with epilepsy, MRS performed *in vivo* has mainly examined the ^{31}P and ^1H nuclei. Conventional MRS software distinguishes short- and long-echo time acquisitions. The latter produces spectra including N-acetyl aspartate (NAA), choline-containing compounds (Cho), phosphocreatine plus creatine (Cr), and lactate [33, 191]. Short-echo time acquisitions include the same metabolites and, in addition, myoinositol, glutamate and glutamine, alanine, glucose, scylloinositol/taurine, and proteins/lipids [10, 28, 86, 137, 161].

Because NAA is located primarily inside neurons and precursor cells, its reduction indicates neuronal loss or dysfunction. Conversely, Cho and Cr are found in both neurons and glial cells. Yet, MRS has been performed mainly in patients with temporal lobe epilepsy, in 60–90% of whom lower NAA concentrations could be observed in the hippocampus [112]. In extratemporal lobe epilepsy, there are only a few studies on the localizing value of MRS. Stanley et al. reported on 20 patients with nonlesional extratemporal epilepsy in whom the relative NAA resonance intensities (i.e., NAA/Cr, NAA/Cho, and NAA/Cr+Cho) were all significantly reduced, particularly in the regions of seizure origin [225]. However, the usefulness of MRS in extratemporal epilepsy has not been confirmed yet.

Functional imaging

Aside from structural imaging for the detection of cerebral lesions, functional imaging constitutes a helpful extension of the presurgical diagnostic workup. Thus, SPECT and PET both exploit the circumstance that an epileptogenic focus in the interictal state receives a smaller blood supply (hypoperfusion in SPECT) and also metabolizes less glucose than normal brain tissue (hypometabolism in PET) [21, 72, 75, 76]. In the ictal state, the contrary applies, i.e., the epileptogenic focus receives a larger blood supply (hyperperfusion in SPECT) and metabolizes more glucose (hypermetabolism in PET) [21, 72, 75, 76].

The most commonly used tracers for both interictal and ictal SPECT are technetium 99m hexamethyl-propy-

lene amine oxime (HMPAO) and technetium 99m ethylene cysteinate dimer (ECD). In ictal SPECT, the tracer is administered intravenously at the beginning of the clinical and/or electroencephalographic seizure onset. A physician or nurse who injects the tracer and video EEG surveillance are needed for this procedure [232]. Even though it appears very complicated and time-consuming, the usefulness of ictal SPECT examination is enormous and justifies the effort, especially in extratemporal epilepsy.

Interictal SPECT in temporal lobe epilepsy has a sensitivity of about 50% and is therefore only of limited value for presurgical workup [72, 232]. In extratemporal lobe epilepsy, its localizing accuracy is even lower [91, 126]. Conversely, ictal SPECT is a very useful tool in presurgical evaluation. In mesiotemporal lobe epilepsy, its sensitivity ranges from 90% to 97% [41, 84, 217]. In extratemporal lobe epilepsy, the localizing accuracy of ictal SPECT depends mainly on the injection delay. The sensitivity in extratemporal lobe epilepsy was 81–90% in various studies [45, 46, 47, 77, 83, 117, 125, 126]. The localizing value of SPECT can be notably improved by coregistration of the interictal and ictal SPECT images, which yields an “ictal difference image” that may be coregistered with a patient’s MRI [117, 147].

Interictal and (rarely performed) ictal PET have been carried out mainly with [^{18}F] fluorodeoxyglucose and [^{11}C] flumazenil [82, 110, 233, 234]. In temporal lobe epilepsy, interictal PET demonstrates hypometabolism in about 60–90% of patients and therefore can be used in presurgical diagnosis [82]. However, PET is less sensitive in extratemporal lobe epilepsies (about 45–60%) and provides few useful data in these forms of epilepsy [82]. For example, its role in localizing the epileptogenic focus in MRI-negative frontal lobe epilepsy is not well established. Although PET may detect frontal focal hypometabolism, the abnormality detected may not correspond to the epileptogenic focus. The hypometabolism may even be found in regions outside the frontal lobe [82].

Neuropsychological evaluation

Every patient with temporal or extratemporal epilepsy needs thorough preoperative neuropsychological examination. The following functions are generally tested: memory (mainly a function of the temporal lobe), learning, IQ, language lateralization, motor skills, visuo-perceptive and visuoconstructive functions, attention and concentration, and verbal and nonverbal fluency [102, 154, 168]. Although the test batteries may vary from center to center, some, such as IQ testing with the Wechsler Adult Intelligence Scale, are generally accepted and established [97, 98, 251]. In addition, some tests are administered to find cognitive deficits of the lobe from which seizures originate. Tests for assessing frontal lobe functions include the Wisconsin Card Sorting, Design Fluency, Stroop, tower, trail-making, finger-tapping, and Purdue or Grooved Pegboard tests [19, 43, 69, 102, 118,

135, 158, 175, 224, 228, 235]. The Rey-Osterrieth Complex Figure Test and somatosensory tests such as two-point discrimination are used to assess parietal lobe function [71, 98, 118, 153, 177]. Memory tests focus on learning and retention of both verbal and nonverbal material. The most commonly administered test is the original or revised Wechsler Memory Scale [98]. Apart from word pairs and story recall, a list learning test such as the California or the Rey Auditory verbal learning tests is often used [98]. Tests for the assessment of language skills include the Western Aphasia Battery, Boston Diagnostic Aphasia Examination, and Boston Naming tests [98, 102, 236]. The last named is also used to assess function of the temporal neocortex [98, 99, 100, 102, 236].

Invasive evaluations (phase II)

If the seizure characteristics and results of phase I evaluations are concordant, patients can be directly passed on to neurosurgery. In the case of mesial temporal lobe epilepsy, this can be done more and more often, thanks to modern imaging procedures [37, 105, 231]. However, when noninvasive presurgical workup fails to delineate the epileptogenic zone adequately, invasive EEG may become necessary. In addition, if the side and site of seizure origin imply overlap with an eloquent speech and/or memory area, an amobarbital (Wada) test may become necessary.

Invasive electroencephalographic recording

The proportion of patients undergoing intracranial electrode implantation varies among epilepsy centers [148, 183, 216, 279]. The following indications for invasive monitoring are currently applied: lack of a potentially epileptogenic structural lesion as revealed by MRI, multiple putative epileptogenic lesions (zones), scalp EEG with multifocal or no interictal epileptiform discharges, surface EEG with indeterminate or multifocal seizure onset, discordant phase I findings, and seizure origin as identified by noninvasive procedures appearing diffuse or proximate to an eloquent area (e.g., perirolandic, Wernicke's, or Broca's area). Based on these indications, invasive EEG recording has been performed in 5–20% and 40–70% of temporal and extratemporal lobe epilepsy surgery patients, respectively [218].

If there is reason to assume that the seizures originate in mesiotemporal structures, intracranial EEG can be recorded by means of semi-invasive foramen ovale electrodes [257, 259, 261]. If phase I findings, however, point to an extratemporal or temporal neocortical seizure onset, invasive monitoring is performed by strip and/or grid electrodes and, less often, by depth electrodes. Strip and/or grid electrodes are laid under the dura subsequently to a small craniotomy, while depth electrodes are

Table 4 Accuracy of different intracranial electrodes in localization of seizure origin (modified from [219])

Diagnosis	Grid (%)	Strip (%)	Depth (%)
Lesional	6/11 (55)	3/11 (27)	2/11 (18)
Nonlesional	13/42 (31)	28/42 (67)	1/42 (2)
Medial location	1/23 (4)	20/23 (87)	2/23 (9)
Lateral location	15/26 (58)	10/26 (39)	1/26 (4)
Regional	10/21 (48)	10/21 (48)	1/21 (5)
Focal	9/32 (28)	21/32 (66)	2/32 (6)
Temporal	8/23 (35)	14/23 (61)	1/23 (4)
Extratemporal	11/30 (37)	17/30 (57)	2/30 (7)
Parietal	0	3/3 (100)	0
Frontal	9/17 (53)	8/17 (47)	0
Occipital	2/10 (20)	6/10 (60)	2/10 (20)

placed stereotactically by means of a small craniotomy [120, 148, 149, 216].

The accuracy of invasive electrodes depends not only on the type used but also on the cause of epilepsy and seizure origin. Spencer and Lee analyzed the accuracy of different electrodes in 53 patients with different types and causes of epilepsy (Table 4) [219]. In their study, localization accuracy for lesional and neocortical (in particular frontal) cases was higher with grids than with strip electrodes. The latter, however, localized seizure origin more precisely in nonlesional and mesial cases. These findings are in agreement with numerous other studies [176, 215, 216, 222].

The rate of morbidity when using intracranial electrodes is low (1–2%) and largely restricted to patients with wound infections or, more rarely, hematoma [57, 60, 215, 218]. Due to intracranial subdural electrodes and depth electrodes, the extratemporal origin of seizure can be determined in approximately 70–80% of implanted patients, who can then be considered for operation. Invasive re-evaluation is occasionally necessary after an unsuccessful first evaluation [204].

Amobarbital (Wada) test

Since 1960, intracarotid amobarbital testing (Wada test) has been part of the standard preoperative evaluation of candidates for epilepsy surgery in order to lateralize language and memory function [247]. The intra-arterial injection of sodium amobarbital into the carotid artery (global Wada test) or, more selectively, into the anterior choroidal artery (selective or superselective Wada test) may provide further information on dysfunctional hemispheres so that the risk of postoperative memory deficits can be assessed [223, 247, 262]. While the Wada test is a crucial tool in the presurgical evaluation of temporal lobe epilepsy (particularly when the operation is planned on the speech-dominant side), it does not play an important role in extratemporal epilepsy [101].

Surgical treatment of medically refractory epilepsies (phase III)

If a patient has undergone presurgical evaluation and, having met the criteria detailed above, is still a candidate for epilepsy surgery, the optimal neurosurgical intervention should be discussed in an interdisciplinary seizure conference including epileptologists, neuropsychologists, psychiatrists, and neurosurgeons. Epilepsy surgery interventions are generally divided into the following categories according to indications, underlying pathology, and method and extent of resection:

1. Procedures are classified as causal or palliative. Causal operations (e.g., anterior 2/3 temporal lobectomy or resection of cavernous malformations) have the purpose of removing an epileptic focus so that seizure-free outcome can be achieved. Palliative procedures (e.g., callosal section), on the other hand, aim at either an interruption of seizure spread pathways or resection of secondary epileptogenic pacemakers. Surgical outcome is understandably not as good with palliative operations as with causal operations.
2. On the basis of radiologic findings, a distinction is also made between lesional and nonlesional interventions. The former apply for the removal of radiologically detected structural lesions (so-called lesionectomies of, e.g., tumors, cavernous malformations, etc.), while the latter are performed in patients whose MRIs are normal or show only nonspecific pathology.
3. Furthermore, epilepsy operations may be classified as either resective or nonresective (disconnective). In resective intervention, a variable amount of cerebral tissue is removed (as in lesionectomies or amygdalohippocampectomies). Nonresective (disconnective) operations include callosotomy and multiple subpial transection. The implantation of a vagal nerve stimulator is also a type of nonresective surgery.
4. Finally, procedures are divided into those strictly limited to the removal of epileptogenic foci (individually tailored resections such as partial cortical frontal resection) and those involving more extensive, standard resection (e.g., standard anterior 2/3 temporal lobectomy) independent of the size of the epileptogenic focus. One clearly prefers to minimize the volume of brain resected—even though this means a few patients will require second operation because of unsatisfactory seizure outcome. The more common neurosurgical procedures for epilepsy and their associated seizure outcomes are discussed individually below.

Temporal lobectomy

Removal of the anterior temporal lobe is the most frequent and most successful type of epilepsy surgery. The most common version of this operation is standard anterior temporal lobectomy, which is, however, difficult

to define because of subtle variations from center to center. Some neurosurgeons prefer the Falconer approach, which consists of en bloc resection of the temporal lobe (usually 4.5–6.5 cm from the temporal pole, depending on the side of operation, i.e., a smaller resection is performed on the speech-dominant hemisphere) including the amygdala and hippocampus [35, 59, 241, 248] (Fig. 1). Other surgeons remove variable amounts of the temporal lobe on the basis of intraoperative electrocorticographic findings [68, 237, 238].

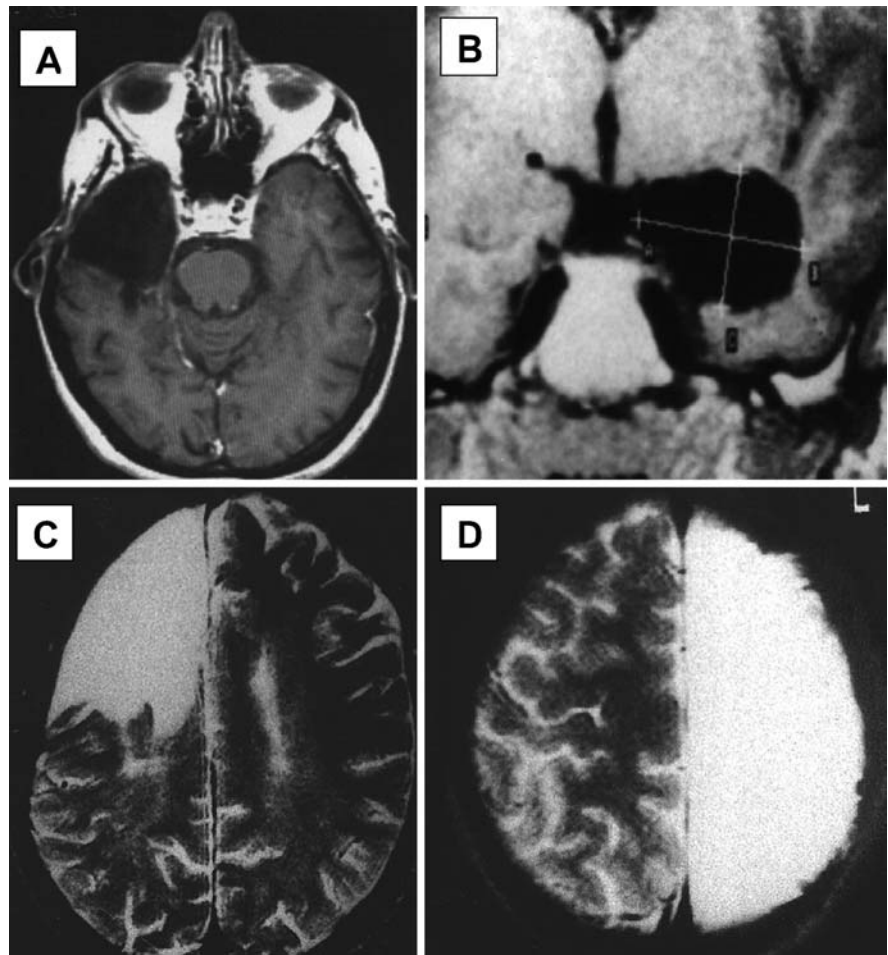
The success rate for seizure control following standardized temporal lobectomy performed for strict indications is up to 80% [51, 52, 94, 95, 210, 212]. Surgical outcome in patients with neocortical temporal lesions may be complicated by the presence of dual pathology in as many as 30% [24, 116, 119]. Major operative complications from standard temporal lobectomy are rare. More common complications include subquadrantic or quadrantic visual field deficits (in >50% of patients), supraquadrantic or hemianopic visual field deficits (2–4%), transient or persistent hemiparesis (4% and 12%, respectively), infections (meningitis or abscess) and epidural hematoma (<0.5% each), transient III or IV nerve palsy (<0.1%), transient anomia for 4–7 days (>20%), persistent dysphasia (1–3%), global memory deficits (1%), and transient psychosis or depression (2–20%) [159, 160]. The mortality of standard anterior temporal lobectomy is <1% [159, 160].

Selective amygdalohippocampectomy

Seizure discharges in the most common form of focal epilepsies, mesial temporal lobe epilepsy, arise almost exclusively from the amygdala, the hippocampus, and, to some extent, the parahippocampal gyrus [256]. This fact immediately suggests that a resection limited to these structures might abolish the seizures. The first selective resections of these mesial temporal lobe structures go back to Paolo Niemeyer [145]. In 1958, he reported on the selective removal of the amygdala and hippocampus through a transcortical approach. Although the results were promising, this method of operation fell into oblivion because of other developments.

Then, in 1975, selective amygdalohippocampectomy by a trans-sylvian approach was developed in Zurich by the neurosurgeon Yasargil and the epileptologist Bemoulli, whose initial work was continued by Wieser [255] (Fig. 1). In this procedure, after removal of the amygdala, the anterior part of the hippocampus and part of the parahippocampal gyrus are removed. In addition to these mesial structures, the most important afferent pathway (entorhinal area) and the pathways of seizure spread (uncinate fasciculus, anterior commissure) are interrupted, which also contributes to the good postoperative results [200]. In a retrospective study of 369 patients with selective amygdalohippocampectomy followed up for at least 12 months (average 85.2), 67% were seizure-free or had auras only. A further 11% had no more than one or

Fig. 1A–D Different types of epilepsy surgery. **A** Temporal lobectomy, **B** selective amygdalohippocampectomy, **C** frontal lobectomy, and **D** anatomical hemispherectomy



two seizures per year, and 15% showed reductions in seizure frequency of at least 90%; however, 8% obtained no substantial improvement [264]. Similar results have been reported in other studies analyzing seizure outcome after amygdalohippocampectomy with different approaches [85, 108, 150, 155, 156, 210, 278, 282]. Factors correlating with good outcome were the presence of a structural lesion (particularly severe hippocampus sclerosis), history of febrile convulsions, extensive resection of the hippocampus and especially of the parahippocampal gyrus, presurgical lack of contralateral epileptogenic foci, brief seizures (particularly with origin in the most anterior part of the mesial structures), and—in ictal discharges with contralateral propagation—late propagation to the contralateral hemisphere [199, 200, 259].

Extratemporal resections

In contrast to the commonly applied, standard, anterior 2/3 temporal lobectomy discussed above, complete removal of the frontal, parietal, or occipital lobes is nowadays hardly ever carried out (Fig. 1). The current surgical treatment of extratemporal epilepsy mainly includes partial cortical resection of the frontal, parietal, or

occipital lobe and is limited to the epileptogenic focus [166].

In a large series of 75 patients operated on for frontal lobe epilepsy, 64% were postsurgically seizure-free, 12% had only rare seizures, 16% showed worthwhile reductions in seizure frequency, and 12% showed no worthwhile reduction [195]. The 26 patients with tumors (only two malignant) as the cause of seizures had the best results (81% seizure-free). In contrast, only 50% of the patients without lesions became seizure-free. Similar results have been reported by other centers [61, 62, 144, 187, 208, 253, 283].

In 39 patients with parietal lobe epilepsy surgery, 52% were postsurgically seizure-free and 30% had seizure frequencies reduced more than 90% [151]. Complications included transient sensorimotor deficits or mild aphasic syndromes (in 20% of the patients), permanent sensorimotor deficits (in 12%), and worsening of preoperative sensory deficits (in 15%) [189, 190]. Rare complications following parietal lobe surgery are transient lower quadrantal visual field deficits and right-left disorientation and a partial Gerstmann's syndrome [189, 190].

In 30 patients with occipital lobe epilepsy, 71% were seizure-free after the operation, and 18% had seizure reduction of more than 90% [151]. Visual field deficit is

the major complication following occipital lobe surgery [186]. Homonymous hemianopsia was present in 76% of cases, over two thirds of whom had partial visual field deficits preoperatively [186].

Compared with nonlesional cases, lesionectomies have a greater likelihood of producing seizure freedom, in particular if they include margin resection [16, 26, 203]. However, epilepsy surgery in patients with negative MR scans (nonlesional cases) may also yield good seizure outcome. In a study by Siegel et al., 20 of 25 patients with nonlesional neocortical, mainly extratemporal epilepsy became postsurgically seizure-free or had only rare seizures following cortectomy [205].

Callosotomy

Transection of the corpus callosum is probably the best example of a palliative operation. Callosotomy is intended to interrupt the pathways of seizure spread or interhemispheric synchronization [15]. Van Wagenen made the observation that epileptic patients who subsequently sustained a stroke involving the corpus callosum often had improvement in their seizure disorders; and in 1940 he and Herren reported a series in which the corpus callosum was intentionally divided for the treatment of intractable epilepsy [243]. In the early 1960s, Bogen reported a small series of similarly operated patients with encouraging results [12, 13, 14], and Luessenhop described comparable success in three of four children [123, 124]. In 1971, Wilson chose this procedure as an alternative to hemispherectomy in a 9-year-old boy with infantile hemiplegia and began compiling a series of 20 patients that ultimately revealed the efficacy of the procedure, warranting its wider application [74, 169, 271, 272, 273, 274, 275].

Callosal section may either be limited to the anterior half (or 2/3) of the corpus callosum or include some or all of the posterior half. Total callosotomy is rarely performed (in one- or two-stage operation) to avoid complications such as mutism, apraxia, and frontal lobe dysfunction [179, 180]. In the early years of callosotomy, division of additional structures important for interhemispheric seizure propagation, such as the anterior commissure, fornix, and posterior hippocampal commissure, was performed in the same operation [179, 180]. The indications for this palliative intervention are infantile hemiplegia, Lennox-Gastaut syndrome, Rasmussen's encephalitis, and multifocal bilateral epilepsy [65, 66, 67, 179, 180, 211, 214, 280].

As far as seizure types, status epilepticus and drop attacks respond especially well to callosotomy. Our own study of 104 callosotomy patients at the Dartmouth-Hitchcock Medical Center, New Hampshire, USA found that 66% of patients with status epilepticus and 52% of those with drop attacks prior to surgery had none after the callosotomy [179, 180]. Complications of callosotomy included acute disconnection syndrome lasting days to weeks (in 90% of patients), sensory disconnection

Table 5 Different techniques for hemispherectomy (modified from [245])

Anatomical hemispherectomy [36, 109, 254]
Modified hemispherectomy [1]
Functional hemispherectomy [167]
Hemidecortication [89]
Hemicorticectomy [277]
Hemispherotomy [39]
Peri-insular hemispherotomy [244]

(>90%), split brain syndrome (30% transitory and 3% persistent), paresis or apraxia of the left arm or leg (about 15%), disorder of written language and/or mutism (6–15%), and cognitive deficits (about 10%) [159].

Hemispherectomy and multilobar resections

Further therapeutic options in patients with severe drug-resistant epilepsy and large multilobar or hemispheric epileptogenic lesions include multilobar resection and hemispherectomy. The latter is a surgical procedure in which a cerebral hemisphere is either anatomically removed or made nonfunctional by disconnection. Anatomic hemispherectomy involves a complete hemispheric corticectomy with or without removal of the basal ganglia, sparing both the hypothalamus and the diencephalon [109, 132, 245, 254, 276] (Fig. 1). Anatomic hemispherectomy has been performed both as a single operation and in multiple sittings [36, 70, 109, 146, 167]. After superficial cerebral hemosiderosis was recognized as a late, severe complication of anatomic hemispherectomy, other surgical techniques were developed [1, 39, 89, 165, 167, 244, 245, 277] (Table 5).

At present, porencephalic cysts and hemimegalencephaly, large cortical dysplasias, Rasmussen's encephalitis, and the Sturge Weber syndrome are considered to be indications for multilobar resection and hemispherectomy. Furthermore, the latter is almost exclusively performed in patients who already have major preoperative deficits such as hemiplegia. In this subset of patients, seizure freedom can be achieved in over 90–95% of cases [245, 246, 277]. A series of 68 patients with hemispherectomies yielded very good results: 80% were postsurgically seizure-free (more than half no longer needed antiepileptic drugs) and 14% had seizure reduction of more than 90%. Despite these excellent results, the decision to perform such large resections should only be made cautiously. Furthermore, extensive presurgical evaluation must be carried out to lessen the likelihood of major postoperative deficit (e.g., pronounced hemiplegia).

Multiple subpial transection

Multiple subpial transection (MST) is a relatively new palliative surgical technique developed for medically

refractory partial epilepsy emanating from an eloquent region such as the speech area or motor sensory cortex [88, 139, 140, 143]. The technique of MST requires a special knife-like instrument with which tangential intracortical fibers mediating seizure propagation are interrupted, while vertical afferent and efferent connections subserving essential cortical functions are preserved [139]. The MST can also be combined with cortical resection. In a series of 100 patients with MST, 48% were postsurgically seizure-free, 13% had only rare seizures, 20% had worthwhile improvement in their seizure situations, and 19% had no benefit. Other studies yielded similar results [88, 141, 143, 185, 220]. In 16 patients with Landau-Kleffner syndrome treated with MST and resective surgery, 75% became seizure-free and 44% had recovered age-appropriate language [143]. Predictors for good seizure outcome were the diagnosis of Landau-Kleffner syndrome and the combination of MST with simultaneous partial cortical resection [209, 281]. In a series of 97 patients, permanent complications occurred in 4% and included basal ganglia hemorrhage in one patient, hemorrhagic infarct with dysphasia in another, infarction of the precentral region in a third, and foot drop in a fourth. Transient complications occurred in 7% and included mild contralateral weakness in five patients, cortical sensory loss in one, and dyslexia in another [142].

Vagal nerve stimulation

The rationale of electric stimulation of the vagal nerve (VNS) for palliative epilepsy therapy is based on findings from animal experiments. Electric impulses are generated in a stimulator device, similar to a pacemaker, which is implanted underneath the clavicle and conducted through a wire electrode directly onto the vagal nerve in the neck [133, 267]. The VNS is indicated in patients with medically refractory partial epilepsy who are not good candidates for resective surgery. A large, multicenter study found that 37–43% of the patients had more than 50% reduction in seizures with VNS [30, 38, 133]. This technique seems to be particularly effective after prior callosotomy (Roberts and Siegel, unpublished data). Complications of VNS included voice alteration, increased coughing, paresthesia, dyspnea, dyspepsia, and laryngismus [6, 73].

Gamma knife radiosurgery

Stereotaxic radiosurgery using the gamma knife has been performed for the last 40 years in the treatment of vascular malformations and brain tumors. Recently, radiosurgery has also made an entrance in epilepsy surgery, particularly for mesial temporal lobe epilepsy syndrome. In the latter, gamma knife surgery delivers a focused dose of radiation to the mesial temporal structures. A recent study analyzed 25 patients treated with the gamma knife instead of open neurosurgical amygdalo-

hippampectomy [173]. Of the 16 patients with sufficient follow-up observation, 13 (81%) became seizure-free.

While gamma knife treatment might be useful in patients who would otherwise undergo mesial temporal lobe resection, it does not yet play an important role in the treatment of extratemporal epilepsy. Today, the gamma knife probably has its major application in the treatment of hypothalamic hamartoma, in which the postsurgical results of a multicentric study are very promising: 80% seizure freedom or improvement [173]. While the advantage of gamma knife—avoiding craniotomy—is obvious, its problem lies in the fact that seizure freedom or reduction usually does not set in till nearly a year after the procedure. This obviously makes it more difficult for the treating physician to recommend, as he must offer patients the choice between operation with usually instant reduction of or freedom from seizures and therapy avoiding craniotomy but after which the seizures persist for at least several months.

Conclusion

Thanks to today's modern imaging examination techniques and especially to the common use of intracranial electrodes for localizing seizure foci, more and more patients with partial epilepsy can be treated microsurgically. The results of such neurosurgical therapies are very good, particularly with mesial temporal lobe epilepsy. In recent years, good results (60–70% seizure freedom) have also been achieved in extratemporal epilepsy surgery, so that such procedures can now be recommended for carefully selected patients.

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