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### Summary

Epilepsy surgery is playing an increasingly important role. In one part this is due to the considerable improvement in structural and functional imaging and electrophysiological techniques, including EEG long-term monitoring. The other reasons are a better understanding of the pathophysiology of those epileptic disorders, which are amenable to surgery, and refinements in surgical techniques. Today reasonably reliable prognosis can be made prior to the recommendation of surgery based on worldwide collected inclusion and outcome data.

Careful and knowledgeable presurgical evaluation of candidates of epilepsy surgery still remains the most important step. Today a considerable number of patients can undergo successful surgery without invasive intracranial presurgical procedures, resulting in an improved cost-effectiveness and in a growing utilization of epilepsy surgery in countries with limited resources. However, for extratemporal MRI-negative epilepsies invasive examinations are necessary.

Intraoperatively three main approaches help to tailor resective epilepsy surgery. (i) Intraoperative recording and stimulation (including evoked potentials), (ii) brain surgery in local anesthesia with the patient awake if surgery in or close to “eloquent” cortex is necessary, and (iii) intraoperative MRI control, mainly to assure radical resection of the intended structures.

An overview of the presently published outcome figures of various epilepsy surgeries is attempted. Possible future scenarios, including radiosurgery, are critically discussed. Some palliative procedures, such as corpus callosotomy, for certain patients, who are not candidates for curative resective epilepsy surgery, are briefly dealt with. Quality-control and multidisciplinary and world-wide collaboration are emphasized.

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**Key words:** Epilepsy surgery, presurgical evaluation, structural and functional imaging, electrophysiological techniques, selective Amytal memory test, postoperative results, radiosurgery

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### Epilepsiechirurgie: Gegenwärtiger Stellenwert und zukünftige Entwicklungen

Der Epilepsiechirurgie kommt eine stetig wachsende Bedeutung zu. Einerseits ist dies bedingt durch die beachtlichen Verbesserungen in den strukturellen und funktionellen bildgebenden Diagnose-Verfahren und elektrophysiologischen Techniken, wie EEG-Langzeit-Monitoring. Andererseits liegen die Gründe in einem besseren Verständnis der Pathophysiologie jener Epilepsieformen, die mittels Epilepsiechirurgie erfolgreich behandelt werden können, aber auch in verbesserten neurochirurgischen Techniken. Heute können vor einer epilepsiechirurgischen Behandlung ziemlich zuverlässige Prognosen abgegeben werden, die auf weltweit gesammelten Outcome-Studien beruhen.

Nach wie vor von vorrangiger Bedeutung ist die sorgfältige und nach dem letzten Stand des Wissens durchgeführte prächirurgische Abklärung, wobei heute eine grosse Zahl von Patienten ohne invasive Abklärung erfolgreich behandelt werden kann. Dies führt zu einer verbesserten Kosten-Nutzen-Rechnung und damit zu einer Zunahme der Epilepsiechirurgie auch in Ländern mit limitierten Ressourcen. Das gilt aber natürlich nur für bestimmte Epilepsieformen. Für extratemporale Epilepsien ohne strukturellen Befund in der Magnetresonanztomographie (MRT) sind invasive Abklärungen weiterhin notwendig.

Intraoperativ haben drei Entwicklungen zur Verbesserung der individuell “massgeschneiderten” resektiven Epilepsiechirurgie beigetragen: (i) intraoperative Ableitungen und Elektrostimulationen des Gehirns (unter Einbezug evozierter Potenzial-Techniken), (ii) Operationen am wachen Patienten in Lokalanästhesie, wenn in oder in der Nähe von funktionell “hochwertigen” Regionen operiert werden muss, und (iii) intraoperatives MRT um sicherzustellen, dass die Resektion die gewünschten Strukturen/Areale entfernt hat.

Wir geben einen kurzen Überblick über die publizierten Ergebnisse der verschiedenen epilepsiechirurgischen Eingriffe und diskutieren kritisch die Ergebnisse der Radiochirurgie, besonders Gamma-Knife. Ebenfalls besprochen werden einige palliative epilepsiechirurgische Methoden, besonders die vordere Balkendurchtrennung. Auf die Notwendigkeit der Qualitätskontrolle sowie die wachsende Bedeutung einer multidisziplinären und weltweiten Zusammenarbeit wird hingewiesen.

**Schlüsselwörter:** Epilepsiechirurgie, prächirurgische Abklärung, strukturelle und funktionelle Bildgebung, elektrophysiologische Techniken, selektiver Amytal Gedächtnis-Test, postoperative Ergebnisse, Radiochirurgie

## Chirurgie curative de l'épilepsie : rôle actuel et développements futurs\*

La chirurgie curative de l'épilepsie prend une importance grandissante. Cette évolution est en partie imputable aux progrès considérables accomplis dans l'imagerie fonctionnelle et les techniques électrophysiologiques, y compris le monitoring de longue durée par EEG. A cela s'ajoute que grâce à la chirurgie, on comprend mieux la pathophysiologie des troubles épileptiques susceptibles d'amélioration et enfin, les techniques opératoires ont été considérablement affinées. Il est désormais possible d'établir des pronostics assez fiables sur la base des données d'inclusion et de résultats recensées dans le monde entier avant de recommander une intervention.

Mais le plus important élément reste une évaluation préopératoire minutieuse et pointue des candidats à une intervention de chirurgie curative de l'épilepsie. Aujourd'hui, un nombre considérable de patients peuvent faire l'objet d'une intervention chirurgicale réussie sans devoir subir des procédures intracrâniennes invasives avant l'opération. Il en résulte une meilleure efficacité en termes de coûts et le recours grandissant à la chirurgie curative de l'épilepsie dans les pays qui ne disposent que de ressources limitées. Toutefois, les examens invasifs restent indispensables pour les épilepsies extratemporales avec un résultat négatif à l'IRM.

Au plan intraopératoire, trois approches majeures contribuent à façonner la chirurgie résective de l'épilepsie. (i)

Enregistrement et stimulation intraopératoires (y compris potentiels évoqués), (ii) chirurgie du cerveau sous anesthésie locale sur le patient conscient si l'intervention doit être pratiquée dans ou à proximité du cortex « éloquent » et (iii) contrôle par IRM en cours d'opération, avant tout pour assurer la résection radicale des structures que l'on entendait supprimer.

Nous tentons de faire un tour d'horizon des résultats jusqu'ici publiés au sujet de différentes méthodes de chirurgie de l'épilepsie. Des scénarios envisageables pour l'avenir, y compris la radiochirurgie, sont discutés sous un angle critique. Certaines procédures palliatives sont brièvement abordées, par exemple la callosotomie du corps calleux pour les patients qui ne sont pas candidats à une résection par chirurgie curative de l'épilepsie. L'importance du contrôle de la qualité et de la collaboration multidisciplinaire et mondiale est soulignée.

**Mots clés:** Chirurgie de l'épilepsie, évaluation pré-chirurgicale, imagerie structurelle et fonctionnelle, techniques électrophysiologiques, Amytal memory test sélectif, résultats postopératoires, chirurgie radiale

## Criteria for and principles of epilepsy surgery

In general the criteria for epilepsy surgery formulated by Walker are still valid. Modifications concern (a) the demand for early surgery, at least in certain epilepsy syndromes, such as Mesial Temporal Lobe Epilepsy (MTLE), (b) "palliative" surgery, and (c) a more liberal indication in children. For "curative" (= "causal") epilepsy surgery the following criteria have to be met: (a) focal or regional seizure onset, (b) pharmaco-resistance, (c) seizures represent a severe handicap, (d) seizures exist for at least 2 years without tendency for remission and despite adequate medical treatment, (e) sufficient general and mental health state of the patient who is sufficiently motivated and compliant in order to collaborate pre-, intra- (if necessary) and postoperatively.

Surgery for epilepsy is performed either with a "curative" or a "palliative" indication: "Curative" aims at complete freedom of seizures by the complete resection of the seizure generating area (see **Figure 1**) "Palliative" aims at an amelioration of the seizure tendency, while seizure-freedom is not expected, although it can occur. "Palliative" procedures consist of the resection of secondary "amplifier structures" (as is the case in palliative amygdalohippocampectomy), or the transection of pathways important for spread of the seizure discharges (as is the case in callosotomy, and multiple subpial transection).

The criteria for "curative" selective amygdalohippocampectomy include (a) unequivocal unilateral medial temporal focal seizure onset at these structures associated with typical clinical symptoms and (b) contralateral hippocampal functions intact (special neuropsychological testing for learning and memory performance, selective temporal lobe Amytal testing and presence of signs indicative of hippocampal atrophy and/or Ammon's horn sclerosis). A "palliative" operation of this type might be indicated in patients with an inaccessible primary epileptogenic zone, i.e. if the primary seizure generating zone in the lateral posterior temporal neocortex cannot be removed without anticipated intolerable functional deficit, and if the ipsilateral hippocampal formation is rapidly involved by the ictal discharges acting as a "secondary pacemaker".

Furthermore epilepsy surgery can be categorized into (a) lesion-oriented surgery, (b) epilepsy-oriented lesional surgery, and (c) surgery for epilepsy sensu stricto. Finally it can be described under the category "standardized interventions" (such as anterior temporal lobe resection, selective amygdalohippocampectomy, anterior corpus callosotomy) and individually "tailored surgical interventions." It is obvious that also so-called standardized operations are most often somewhat tailored, based on preoperative findings as well as on intraoperative electrocorticography and other intraoperative neurophysiological tests (functional mapping). Individually tailored operations comprise topectomies and some larger resections (**Figure 2**).

Careful and knowledgeable presurgical evaluation of candidates of epilepsy surgery still remains the most important step.



Figure 1: Concept of the epileptic focus with its surrounding zones. Note that the lesional zone, the primary epileptogenic or seizure onset zone, the irritative zone, and the symptomatogenic zone can have different location and size. The primary epileptogenic or seizure onset zone is that tissue which has to be removed in order to obtain freedom of seizures. The irritative zone is that from which interictal EEG spikes can be recorded. The symptomatogenic zone is that which is responsible for the primictal seizure symptoms. If the seizure onset is in a so-called “silent” brain region, the primictal signs and symptoms might arise from hodologically related brain sites, perturbed by seizure propagation.

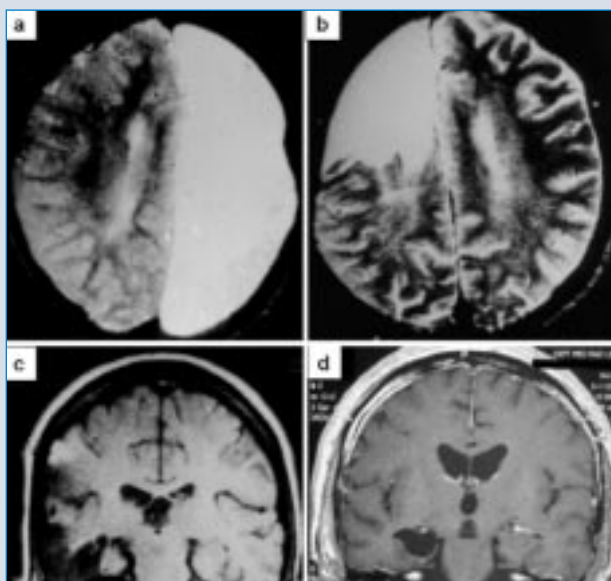


Figure 2: Magnetic resonance images depicting examples of various epilepsy surgeries. (a) Hemispherectomy in a patient with Rasmussen's encephalitis. (b) Frontal lobe resection. (c) Tailored lateral-inferior temporal lobe resection sparing the hippocampus. (d) Selective amygdalohippocampectomy with trans-Sylvian approach [21].

Alternative and experimental treatment options, such as Vagus Nerve Stimulation (VNS), deep brain stimulation (DBS) and radiotherapy for certain epilepsies, have enriched the armamentarium.

The prototype of a surgically amenable syndrome is mesial temporal lobe epilepsy (MTLE). MTLE is frequent and often drug-resistant [1]. It is widely recognized and has been elaborated fairly precisely in terms of clinical signs and symptoms including neuro-psychological and psychiatric aspects, electrophysiological characteristics, morphological and functional imaging findings, etiological and pathophysiological mechanisms, clinical course, and response to treatment, both to antiepileptic drugs (AEDs) and to surgery. The most characteristic feature is its unique pathophysiology, i.e. hippocampal sclerosis.

Without surgery the prognosis of medically refractory patients with MTLE is relatively poor. Both, severity and frequency of seizures may increase, and memory may decline, what may result in severe psychosocial disturbances. Early surgical intervention, i.e., relief of disabling seizures before the negative consequences of MTLE interfere critically with vocational and social development, results in best psychosocial outcome and should be envisaged. With the help of modern neurophysiology, including radiotelemetric long-term seizure monitoring and modern structural and functional imaging methods, today the diagnosis of MTLE can be often made without resorting to invasive methods, i.e., the majority of candidates for sAHE can be assessed non-invasively or at least semi-invasively with foramen ovale (FO) electrodes. Particularly, if lateralization is a problem, “semi-invasive” FO electrodes may be very helpful (see Figure 3).

Surgical therapy in medically refractory patients with MTLE is highly effective and renders about 80% of patients seizure-free. Most centers have modified TL surgery in MTLE with the goal to resect mesial TL structures more radically and to minimize lateral TL resection. Selective amygdalohippocampectomy, the so-called Spencer operation (resection of mesial temporal structures, of temporal pole and of only a small amount of anterior lateral temporal cortex) have been strongly advocated in MTLE. There is evidence that sparing of the lateral TL cortex has advantages in terms of neuro-psychological outcome and that originally hypometabolic lateral TL structures show a trend for normalization of their metabolism. In well-chosen candidates for amygdalohippocampectomy, with an already present unilateral material-specific memory and learning deficit, postoperatively no significant additional deficits occur and the contralateral material-specific memory performance usually increases. Patients without pre-existing memory deficits and in particularly those not becoming seizure-free following left TL resections, usually worsen in their memory. For a better prediction of the postoperative memory and learning in patients considered to be at risk, selective TL memory Amytal tests are useful (see Figure 4)

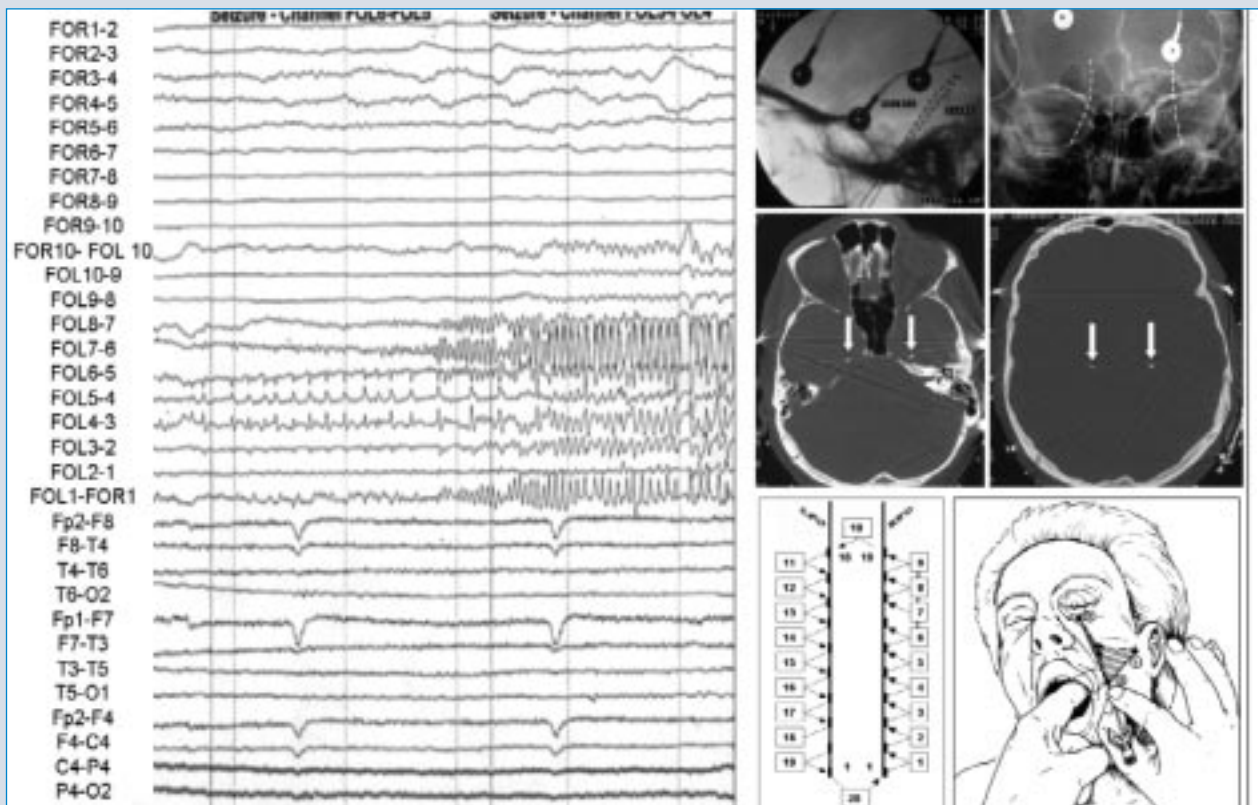


Figure 3: Example of a foramen ovale (FO) electrode recorded seizure with left mesio-temporal onset. Phase reversal of the initial spike train is in the contact 5 of the left FO electrode (FOL5). The anatomical locations of the FO electrodes are depicted in the lateral and antero-posterior x-rays (top, right) and CT scans (arrows). Each FO electrode contains 10 contacts, numbered 1 to 10 from the tip. Recordings from the FO electrodes are in a closed chain (as indicated in the scheme, bottom, middle). At the bottom right the insertion of a FO electrode is illustrated following the technique of Kirschner and using the landmarks of Härtel [22].

### Selective Temporal Lobe Amytal Memory Test

To predict the postoperative memory performance following uni-lateral selective amygdalohippocampectomy (sAHE) we have developed and steadily improved the so-called Selective Temporal Lobe Amytal Memory Test (STLAMT) with short-term inactivation of the to-be-resected brain structures and neuropsychological testing of the effects of this inactivation [2]. Three methods were used: (1) the so-called temporary balloon occlusion distal to the origin of the anterior choroidal artery (acha), (2) the superselective injection of Amytal into the acha, and (3) the injection of Amytal into the P2 segment of the posterior cerebral artery. During the last years method 2 was preferred and a co-injection of Amytal and SPECT-tracer (HMPAO) was realized. Together with behavioral and EEG-monitoring (preferentially with foramen ovale- and/or depth electrodes) the co-injection and subsequent SPECT allow for a precise determination of the inactivated structures. 108 STLAMT have been performed at the University of Zurich without complications. STLAMT allows for a reliable prediction of postoperative memory performance following sAHE. The refinements enable us to interpret individual test data with high confidence. Recent research projects

study to which degree the STLAMT can be substituted by fMRI and special PET activation studies [3].

### Microsurgery and outcome of selective amygdalohippocampectomy

The term “selective amygdalohippocampectomy” (sAHE) is not entirely correct, since it does not denote the removal of the parahippocampal gyrus, which also is partly resected. The sAHE is a fairly standardized operation, as described by Yasargil et al. [4] and Yonekawa et al. [5]. Following a modified pterional craniotomy the trans-Sylvian route – with a cortical incision of 1-2 cm lateral to the M-1 segment and anteromedial to the M-2 segment into the superior temporal gyrus – has been adapted to gain access to the tip of the temporal horn. The amygdala is removed piecemeal both by rongeur (to provide histological specimens) and by gentle suction. By use of the so-called keyhole technique, the hippocampus and the more anterior parts of the parahippocampal gyrus are then resected en bloc. The resected specimen measures approximately 3.5-4 cm in length, 1.5 cm in width, and 2 cm in depth. In the anteroposterior plane the posterior transection of the parahippo-

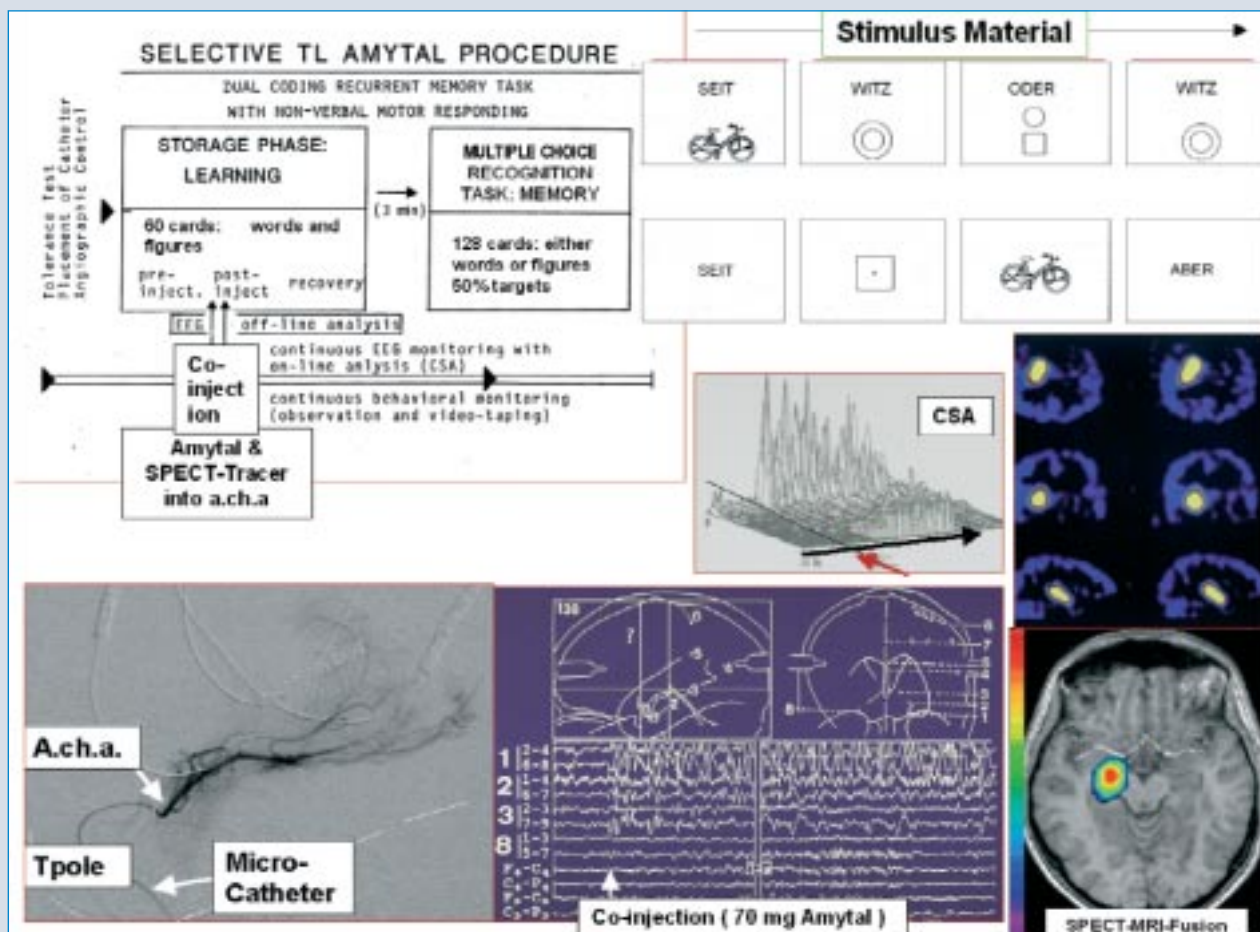


Figure 4: Illustration of the selective temporal lobe Amytal memory test (STLAMT) for preoperative testing of memory in candidates for selective amygdalohippocampectomy (sAHE) to predict postoperative memory performance following unilateral sAHE in patients being at risk for postoperative memory decline. The STLAMT aims at short-term temporary inactivation of the to-be-resected brain structures with neuropsychological testing of the effects of this inactivation. It consists of the superselective co-injection of Amytal and SPECT tracer into the anterior choroidal artery (acha, see left bottom), and the reconstruction of the inactivated brain region (see right bottom) as well as the estimation of the duration of inactivation by measuring the Amytal-induced slow delta activity in the EEG (see middle section, bottom) and the subsequent analysis of the EEG (see CSA, compressed spectral array). The neuropsychological test procedure is a dual coding recurrent memory task with non-verbal motor responding and consists of a storage phase and multiple choice recognition task (see left, top). The stimulus material is illustrated at the top right. During the storage phase 60 cards are presented which consist of both a verbal and nonverbal item. During the recognition task 128 cards are presented which show either a verbal or a figural item. Half of the items have been presented at the storage phase (targets) and half are new. The patient is instructed to press the button if he believes that he has seen a presented item before. This way the verbal and figural memory can be tested separately. The percentages of correct recognitions and of false positives are calculated.

campal gyrus is at the level of the bifurcation of the P-2 segment to form the P-3 segments. This is at the level of the lateral geniculate body, where the fimbria ascends to the splenium to form the crus of the fornix. The mean total size of the resection for 30 randomly selected patients was 7.2 cm<sup>3</sup>.

### Characteristics of the Zurich amygdalohippocampectomy series

Today the Zürich sAHE series comprises 520 patients. In our recent summaries [6, 7] we analyzed the seizure outcome and the antiepileptic drug treatment of 376 patients with sufficient follow-up. More males

(56%) than females (44%) were operated on. The sAHE was on the right in 52% and on the left in 48% of the cases.

The mean age at onset of epilepsy was much earlier in the HS-group compared to the “lesional” group (12±10 versus 23±16 years). Patients with severe HS had their first seizure earlier in life than those with slight HS. In the HS-group the mean preoperative duration of “active epilepsy” was much longer than in the “lesional” group (21±10 versus 7±9 years).

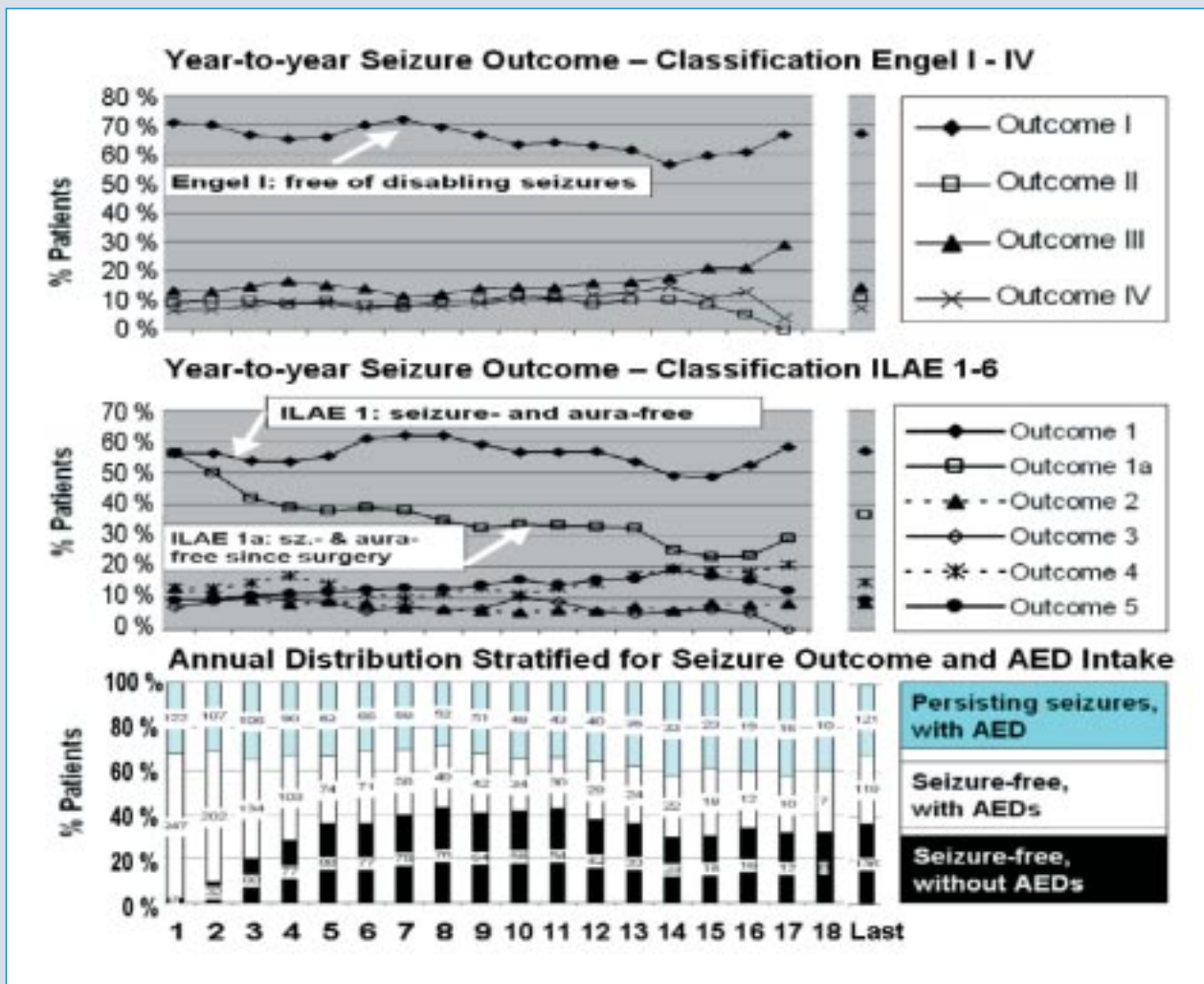


Figure 5: Summary graph with the results of the Zurich selective amygdalohippampectomy series [6, 7], giving the year-to-year seizure outcome for 17 and 18 years respectively and the last available outcome (Last) and stratifying the patients for seizure outcome and AED intake (bottom graph). Minimum follow-up 1 year.

Seizure outcome is classified according to Engel classes I-IV (top graph) and simultaneously according to the new classification proposal of the ILAE (Classes 1-6, see Wieser et al. [9]). Engel Classes I to IV (Top: I, free of disabling seizures; II, rare disabling seizures (“almost seizure free”); III, worthwhile improvement (IIIA, more than 90% seizure reduction; IIIB, prolonged seizure-free intervals amounting to greater than half the followed-up period, but not <2years); IV, no worthwhile improvement (IVA, significant seizure reduction; IVB, no appreciable change and worsening of seizures). Proposed ILAE seizure Outcome Classes 1 to 6, counting seizure days and giving reference to pre-operative baseline. Class 1: Completely seizure free; no auras; 1a: Completely seizure free since surgery; no auras. Class 2: Only auras; no other seizures. Class 3: 1 to 3 seizure days per year; ± auras. Class 4: 4 seizure days per year to 50% reduction of baseline seizure days; ± auras. Class 5: <50% reduction of baseline seizure day to 100% of baseline seizures days; ± auras. Class 6: >100% increase of baseline seizure days; ± auras.

Antiepileptic drug (AED) treatment after amygdalohippampectomy, depicting seizure-free patients (Engel Class I) without and with AEDs, and patients with persisting seizures and AEDs. Mean follow-up was  $7.5 \pm 5.7$  years, 140 pts. had a greater than 10 years follow-up (after Wieser and Häne [7]).

Note that the slightly different outcome figures are due to different inclusion and exclusion criteria and sample size. The seizure outcome study [6] was done with 376 patients, the AED study with a total of 468 patients (excluding 43 patients with “palliative” sAHE and 16 patients without a pathology in the histopathological examination of the resected tissue).

### Postoperative seizure outcome and AED treatment

The seizure outcome was classified according to Engel [8] and the new ILAE (International League against Epilepsy) proposal [9]. Seizure outcome and postoperative AED treatment is shown in Figure 5.

### Neuropsychological data

It is of considerable interest to know whether and to what extent the unilateral sAHE influences postoperative neuropsychological performance. Earlier studies comparing the preoperative and postoperative neuropsychological performance showed that the neuropsychological

chological postoperative results were better in sAHE patients than in patients who underwent an anterior temporal lobectomy [10]. In sAHE patients the performance in postoperative learning and memory performance was the better, the better the postoperative seizure outcome. Furthermore, it was found that the postoperative improvement was mainly due to the improvement of the nonoperated contralateral hemisphere, whereas the performance of the operated hemisphere remained more or less unchanged compared to the preoperative test performance [11, 12]. In no case did we observe a severe global memory deficit or an amnesic syndrome following sAHE. Patients judged to be at risk for a worsening of their memory, however, were routinely submitted to the so-called selective temporal lobe Amytal memory test.

Several psychosocial outcome studies of sAHE patients revealed satisfactory results. Patients were assessed for (a) psychosocial variables: emotional adjustment and coping abilities (depression, tension, fear, shame, disgust, guilt), interpersonal adjustment (social comfort, number of contacts and relationships), adjustment to seizures, and behavioral disturbances (b) vocational and employment career; and (c) "family support".

Overall, postoperative psychosocial functioning of sAHE patients improved. All patients with a postoperative deterioration had persisting seizures, being classified in Engel's outcome categories III and IV. Likewise, the preoperative-to-postoperative comparison of the vocational and employment career revealed that the employment status had postoperatively improved. The rate of employed patients remained the same. There was a strong relationship between the scores of the "psychosocial variables", "employment status", "family support", and "seizure outcome". Patients with a good seizure outcome (Engel Classes I and II) improved postoperatively in all measured psychosocial variables and had significantly better family support. An improvement in the employment status, however, was observed nearly exclusively in only those patients who were completely seizure-free [13].

In summary the sAHE is technically difficult but an appealing operation for carefully selected patients suffering from the syndrome of MTLE. In the hands of our Zurich neurosurgeons (G. Yasargil, Y. Yonekawa), the complication rate in terms of lasting morbidity of this operation is 0.9 %. No visual field deficit was induced. There was no mortality related to sAHE. No unexpected severe memory impairment and, in particular, no postoperative global amnesia have been observed in the Zurich sAHE series. It should, however, be emphasized that all candidates for sAHE undergo exhaustive non-invasive neuropsychological examination and, if the patient is at risk, also selective TL Amytal memory testing. From the operative technique, Yonekawa's recently developed supracerebellar transtentorial approach to posterior temporomedial structures is a major contribution [14].

## Other surgical series including extratemporal epilepsies, palliative corpus callosotomy and Gamma-Knife treatment of epilepsies

There exist many other well documented outcome data of surgical series. Engel et al. [8] have collected worldwide seizure outcome data at the occasion of the Second Palm Desert International Conference on the Surgical Treatment of the Epilepsies, held in Indian Wells, California, in February 1992. The results of this survey on temporal lobe resections are given in **Table 1**.

**Table 1: Results of epilepsy surgery**

Temporal Lobe						
	Before 1985 (%)			1986 - 1990		
		ATL	(%)	AHE	(%)	
Seizure-free	1296	55.5%	2429	67.9%	284	68.8%
Improved	648	27.7%	860	24.0%	92	22.3%
Not Improved	392	16.8%	290	8.1%	37	9%
Total (n, %)	2336	100%	3579	100%	413	100%

Neocortical Resections						
	Before 1985 (%)			1986 - 1990		
		Extratemp. Resections (%)	Lesion-ectomies (%)			
Seizure-free	356	43.2%	363	45.1%	195	66.6%
Improved	229	27.8%	283	35.2%	63	21.5%
Not Improved	240	29.1%	159	19.8%	35	11.9%
Total (n, %)	825	100%	805	100%	293	100%

Results of epilepsy surgery (1992 Second Palm Desert Survey; [8]), shown for temporal lobe and neocortical resections. Note that before 1986 anterior temporal lobe resection (ATL) and selective amygdalohippocampectomy (AHE) were not differentiated (top), and that within the neocortical resections (bottom) no differentiation between non-lesional extratemporal resections and lesionectomies was done.

## Gamma Knife radiotherapy in the treatment of MTLE

As early as 1955 Talairach and colleagues treated epileptic patients by stereotactic implantation of Yttrium 90 into the amygdala and the hippocampus. They reported 44 epileptic patients with this procedure [15]. Steiner and Lindquist analyzing their clinical experience with GK radiotherapy treated arteriovenous malformations (AVM) noted that epilepsy was frequently improved after GK radiotherapy [16]. Seizure cessation often occurred several months before occlusion of the AVM. Lindquist subsequently promoted the idea that GK radiotherapy was perhaps an interesting new approach in the treatment of severe epilepsies,

although his first attempts to treat epileptic nonlesional patients were not encouraging.

Several reasons have led to the evaluation of GK radiotherapy in MTLE. Probably the most important is that the volume of the resection in sAHE is quite small and within the range of GK capability. In March 1993 Régis in Marseilles treated the first patient with medically refractory MTLE by GK radiotherapy at low marginal dose (25 Gy) [17]. In his present study protocol the target is covered by two 18 mm collimators, with a dose of 20 to 25 Gy at the 50% marginal isodose line. The target volume is 6500 to 7000 mm<sup>3</sup>.

Results of 25 patients, treated according to this protocol, and with a follow-up for the entire group ranging between 6 and 72 months have been published.

In summary, efficacy of GK radiotherapy treatment of MTLE appears to be comparable to that of microsurgical resection. However, seizure diminution is remarkably delayed and “radio-induced MRI changes” may

require Cortisone therapy. Definite conclusions about GK radiotherapy efficacy cannot be drawn up to date. The result of the US study must be awaited (Table 2).

Gamma Knife radiotherapy also has been applied in hypothalamic hamartomas and in epilepsies associated with cavernous angiomas and low-grade tumors (Table 2). In addition corpus callosotomy has been performed by GK.

Available results of GK treatment for hypothalamic hamartomas (HH), cavernous hemangiomas and mesial temporal tumors associated with drug resistant epilepsy, tell us that this data are preliminary and that larger series and longer follow-ups are necessary. For HH GK radiotherapy might be as effective as microsurgical resection and very much safer, but GK has delayed action.

With regard to drug resistant epilepsy associated with cavernous hemangiomas the medial temporal location was associated with a higher risk of failure. Central region cavernous hemangioma were seizure free.

**Table 2: Results of Gamma Knife treatment**

	<b>MTLE</b> (n = 20; July 1996 to March 2000 – three European centers – [23])	<b>Hypothalamic hamartomas</b> (n = 30; October 1999 to July 2002 – [24])	<b>Drug resistant epilepsy associated with cavernous hemangiomas</b> (n = 49; July 1996 to March 2000 – five centers – [25])	<b>Drug resistant epilepsy associated with mesial temporal tumors</b> (n = 19; [26])
<b>Median marginal dose</b>	24 ± 1 Gy	17 Gy (range 14-20 Gy)	19.2± 4.4 Gy (range 11.3 to 36 Gy)	17.3 Gy (range 12 to 30 Gy) Irradiation of the presumed epileptic foci (in ccm): mean 6.2 ccm (range 1.1-18 ccm) outside the tumor volume, i.e., 50% isodose volumes surrounding the tumors
<b>Follow-up</b>	2 years	19 patients more than 6 months	mean 23.7 ± 13 months	mean 6.5 years (range 1.7 to 9.7 years)
<b>Outcome</b>	Median seizure frequency at 2 years after GK treatment 0.33 / month. Rate of seizure free patients at 2 years after GK treatment. 13 of 20 (65%).	18 out of 19 patients improved; 7/19 patients had cessation of psychomotor seizures	Rate of patients at the most recent follow up examination: Engel IA 24 patients (49%); Engel IB: 2 patients (4%)	Seizure outcome: Engel Classes I and II: 11 patients (57.9%); Engel III: 7 patients (36.8%); Engel IV: 1 patient (5.3%)
<b>Other clinical and radiological data</b>	Median seizure frequency in the month before GK treatment: 6.16 / month. Median latency in seizure cessation more than 1 year (range 6-21 months). Median delay in the appearance of the MRI changes 10.5 months (range 7-22 months)	Precocious puberty: 20 out of 30 patients. Range of maximum diameter of HH: 7.5 to 23 mm (3 larger than 18 mm)	Mean seizure frequency before GK treatment: 6.9 (±14) / month; Mean duration of epilepsy before GK radiotherapy treatment: 7.5 ± 9.3 years	Histopathology: Low-grade astrocytomas 15 (79%); gangliogliomas 3 (16%); cavernoma 1 (5%). Mean duration of epilepsy before GK radiotherapy 8.6 years (range 0.9-28 years)

**Results of Gamma Knife treatment for MTLE, hypothalamic hamartomas, drug resistant epilepsy associated with cavernous hemangiomas and mesial temporal tumors.**



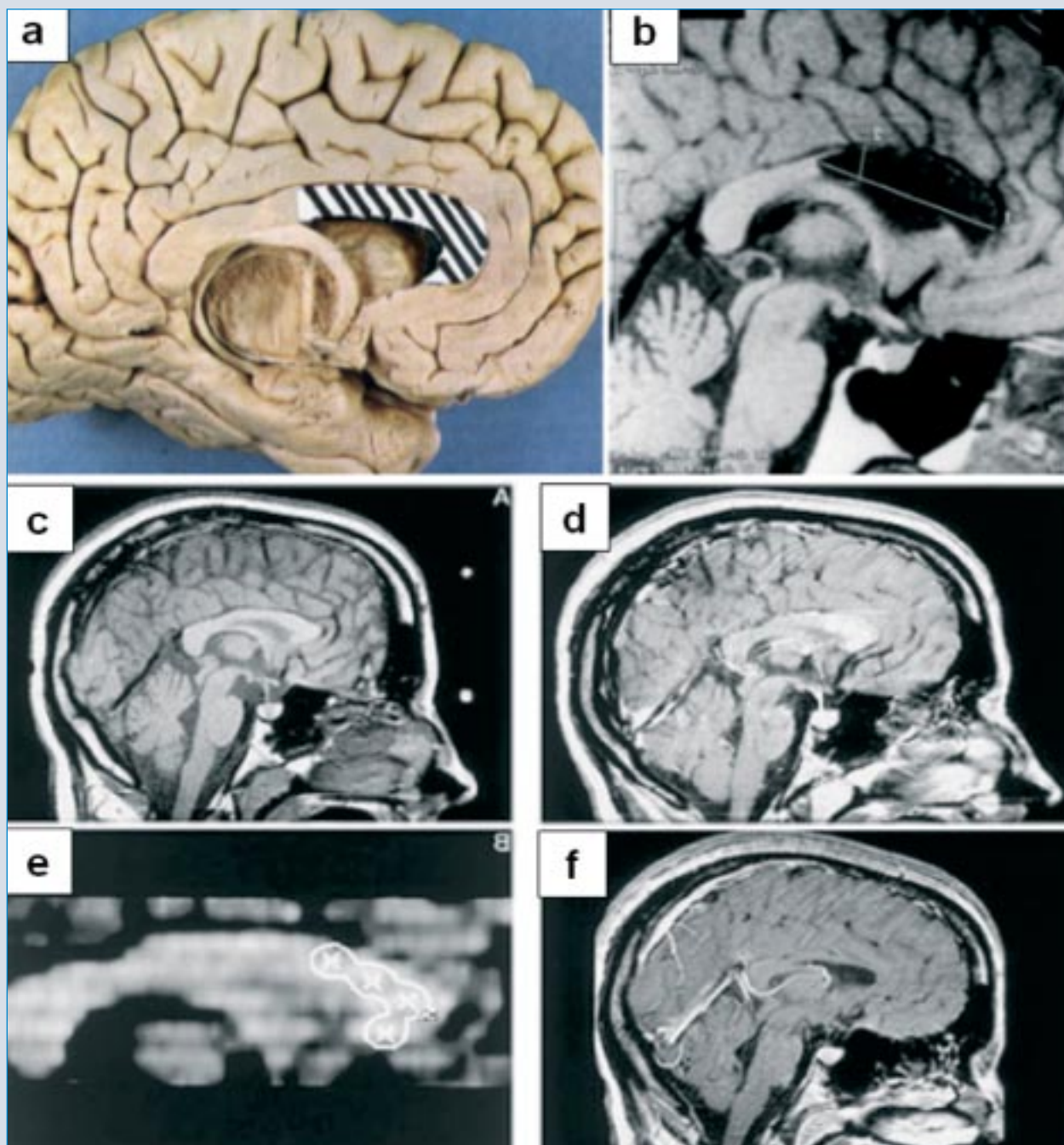


Figure 6: Top: Scheme (a) and postoperative MRI (b) showing an anterior callosal section (performed by Prof. Y. Yonekawa). Bottom: Callosotomy with Gamma Knife: On the MRI (sagittal, T1-weighted; [c]) the GK dosimetry is projected [e] with the isocenters. At the isodose center the dose was 150 Gy. Three months after GK treatment a signal alteration is seen in the target area [d, contrast-enhanced] and 2 yrs after GK treatment a local atrophy is seen [f]. From: Pendl et al. [18], with kind permission.

Most authors do not recommend GK radiotherapy for prevention of bleeding for a cavernoma that has not bled previously. GK radiotherapy can, however, be proposed for the treatment of epilepsy when the cavernoma is located in a highly functional area.

### Corpus callosotomy

Corpus Callosotomy (CCT) is a surgical option for medically uncontrolled secondary generalized epilepsy in appropriate patients. The ideal candidate suffers from sudden drop attacks. It is a palliative procedure and seizure-freedom should not be expected, although rare patients with complete cessation of seizures are reported. From a total of reported CCT patients (1986-1990) 7.6% were seizure-free, 60.9% were ameliorated

and 31.4 % did not profit from CCT [8]. CCT is competing with other palliative procedures, such as VNS. But since Gamma Knife-CCT has now become available, its exact role has to be redefined. Pendl et al [18] treated three patients with stereotactic radiotherapy to ablate the anterior third of the corpus callosum (see **Figure 6**). The patients had intractable epilepsy: two had Lennox-Gastaut syndrome, and one had multifocal epilepsy with atonic, tonico-clonic, and atypical absence seizures. The history of seizures ranged from 20 to 37 years duration. Stereotactic radiotherapy was performed with a cobalt-60 GK using a 4-mm collimator, targeted to the rostrum, genu, and anterior third of body of the corpus callosum. Two patients were treated once with 150 and 160 Gy at maximum, respectively, and one patient was treated in two stages with 50 Gy and then 170 Gy at maximum. Pendl et al. reported that the severity and frequency of seizures were significantly reduced in all three patients. The types of seizures associated with the most improved outcome were atonic and generalized tonico-clonic seizures. The mean follow-up period was 38 months. No complications related to irradiation were recorded except transient headache in one patient. The authors conclude that radiosurgical CCT may be a promising alternative treatment to open callosotomy.

### Current role of radiotherapy in epilepsies

The main limitations of Gamma Knife radiotherapy are the delayed response of between 8 and 15 months and the volume constraints. Nevertheless, there is a strong rationale for investigation of the role of GK radiotherapy in the treatment of medically intractable epilepsy. To explore this potential application, the current outcomes and morbidities associated with established microsurgical treatment as well as the associated advantages and disadvantages of open surgery have to be compared. The more recent positive experience with GK radiotherapy treatment for epilepsy associated with MTLE, cavernous angioma, and hypothalamic hamartoma has to be verified by further studies. Although the benefits of comfort and reduced invasivity of GK radiotherapy treatment can be clearly distinguished, larger series and long term follow up are still required in order to evaluate the future of this peculiar radiotherapeutic approach.

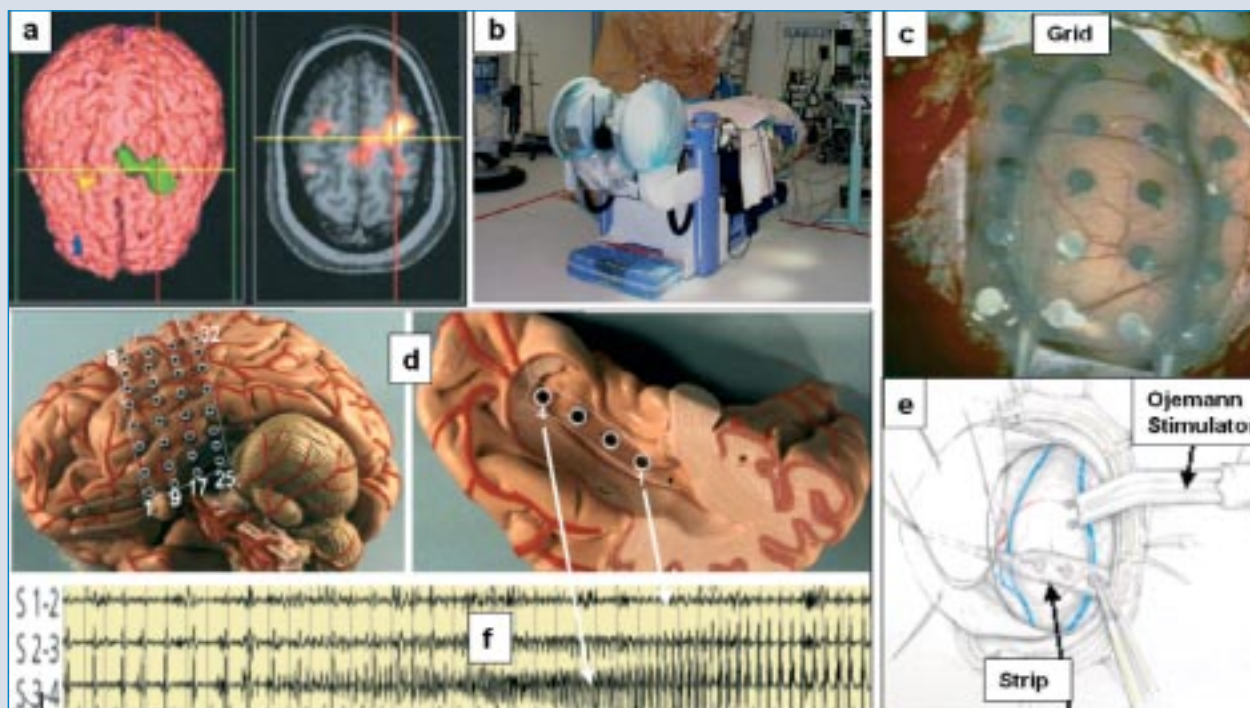
Alternative radiotherapeutic treatment options of epilepsy are already considered advantageous in some conditions where classical microsurgical neurosurgery is limited. Some tumor-associated focal epilepsies of delicate locations (insula of Reil and hypothalamic hamartoma) may profit from radiosurgical approaches, such as the interstitial <sup>125</sup>-iodine radiotherapy of low-grade gliomas by seed-implantation. Arguments for radiotherapy are lower mortality and morbidities with equal efficacy with regard to seizure outcome and qua-

lity of life. In principle radiation is possible by a single therapeutic action and by “fractionated stereotactic precision radiation”. In principle today GK, Linear accelerator and Cyclotron techniques are available and competing. In the field of so-called “non-lesional (non-tumoral) epilepsy surgery” only with the GK technique has a reasonable experience accumulated with at least some – albeit limited – long-term data. Theoretically proton therapy with the proton pencil beam and the spot-scanning technique, recently pioneered at the Paul Scherrer Institute in Villigen/Switzerland, promise certain advantages [19]. However, no data with reference to epilepsies are available. This is astonishing because it has been estimated that worldwide about 27'000 patients in 18 centers have been treated with proton therapy, mainly patients suffering from tumors of the eye and brain skull base, neck and pelvic tumors.

### Intraoperative approaches in epilepsy surgery

Intraoperatively three main approaches help to tailor resective epilepsy surgery.

(i) Intraoperative recording and stimulation (including evoked potentials), (ii) brain surgery in local anesthesia with the patient awake if surgery in or close to “eloquent” cortex is necessary [20], and (iii) intraoperative MRI control, mainly to assure radical resection of the intended structures (see **Figure 7**).



**Figure 7:** Illustration of the elements of modern epilepsy surgery: (a) Mapping the seizure origin delineated by ictal SPECT (SISCOM; from Elger, with kind permission); (b) Intraoperative MRI (Polestar); (c-e) Intraoperative electrocorticography (ECoG) and electrical stimulation (“functional mapping of eloquent cortex”): (c) shows a grid electrode placed over the Rolandic cortex and (e) the electrical stimulation of this area performed with the Ojemann stimulator and a strip electrode to record simultaneously from the vicinity of the stimulated cortex to detect afterdischarges or induced seizures. (d) illustrates the simultaneous placements of a grid over the lateral and inferior temporal lobe and a strip on the intraventricular hippocampus in a patient undergoing selective amygdalohippocampectomy. In (f) a spontaneously occurring hippocampal seizure discharge is shown which originates from the anteriorly situated contacts 3 and 4 of the hippocampal strip electrode.

## Concluding remark

Advanced non-invasive diagnostic tools to delineate epileptogenic lesions and epilepsy related functional deficits and refined EEG techniques to prove epileptogenicity have resulted in better postsurgical outcome figures and in a larger population of difficult-to-treat patients profiting from surgical therapy. In addition, a considerable proportion of patients undergo epilepsy surgery without invasive presurgical evaluation. Lesions including mesial temporal lobe sclerosis and cortical malformations and dysgenesis can be detected to a high degree of confidence with high resolution MRI (T1, T2, FLAIR, diffusion and perfusion techniques). Detection of deficits and functionality of certain brain areas has profited from PET (18F FDG, Flumazenil), selective inactivation of brain regions using Amytal testing with co-injection of SPECT tracers, fMRI and activation PET using  $H_2^{15}O$ . For the location and the size of the epileptogenic area, besides the clinical semiology, electrophysiological techniques (EEG and MEG) and ictal SPECT are the main diagnostic techniques. Both 31P- and 1H-MR-spectroscopy as well as MEG are further remarkable developments. Advanced telemetric long-term monitoring systems are available and complemented by improved EEG analysis methods (such as LORETA and

dipole modeling). These modern diagnostic tools improved the presurgical evaluation and present algorithms for the presurgical evaluation of the most common epilepsy constellations.

Epilepsy surgery is playing an increasingly important role. A better understanding of the pathophysiology of those epileptic syndromes, which are amenable to surgery, and refinements in surgical techniques allow a reasonably reliable prognosis prior to the recommendation of surgery based on worldwide collected inclusion and outcome data. Careful and knowledgeable presurgical evaluation of candidates of epilepsy surgery still remains the most important step.

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