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A longitudinal assessment of seizure outcome and overall benefit from 100 cortectomies for epilepsy

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Abstract

Results of 100 cortical resections for 76 temporal, 23 frontal and one parietal lobe epilepsies were studied in terms of seizure relief and overall benefit. A non-homogenous Markov chain model was used to take into account both the intravariability of post-surgical outcome and the differences in duration of follow-up in a group of patients consecutively operated. The seizure free (SF) state was defined as no seizure in the previous five months at first follow up visit and none in the preceding 12 months at subsequent annual visits. For the whole of the population the SF probability was 82%, 66%, 61%, and 62% at six months, one year, two and five years respectively. A better outcome was found for temporal lobe epilepsy (SF probability: 68% at the fifth postoperative year) than for frontal lobe epilepsy (SF probability: 42% at the fifth postoperative year) with a statistically significant difference. Pre- and postoperative interictal signs and symptoms were classified according to their clinical significance: (*a*) mild handicap—symptoms recognisable but no interference with usual life, and (*b*) moderate or severe handicap—interference with some or all daily activities. The interictal state was considered more impaired after surgery than before in two situations: (*a*) either symptoms, absent before surgery, appeared in the postoperative period involving a moderate or severe handicap, or (*b*) symptoms present before surgery and answerable for a mild or moderate handicap that increased to involve a moderate or severe handicap respectively in the postoperative period. Surgery was considered a major benefit when two conditions were fulfilled—namely, a SF state and no deterioration of the interictal stage when compared with the preoperative period. The probability of obtaining such a benefit was 58%, 51%, 48% and 56% at six months, one year, two and five years respectively. The results suggest that surgery is an effective treatment for more than 50% of longlasting medically intractable epilepsies.

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The outcome of surgical treatment for epilepsy cannot be assessed in terms of seizure improvement alone. One must also consider whether the quality of life after surgery is sufficiently improved to justify the risks imposed by this procedure.[33 46] Moreover, the outcome assessment is complicated by yet unsolved methodological problems. The result is that although surgery for epilepsy is well founded, it is sometimes still questioned.[7] When confronting this problem, two main difficulties are encountered. First of all, the number of seizures may be quite different according to the period of follow up. For example, a seizure free (SF) patient during the first postoperative year could have one or more seizures during the second year and later be free from seizures again.[11] Secondly, surgery interferes with the neurological and psychological interictal state which may be either improved or impaired.[14 15 18 20 22 25 29 34 35 38 44] The results from 100 consecutive cortical resections for intractable partial epilepsy were studied taking these problems into account. The patient group was followed up for a period of five years using a statistical methodology that allowed for the possible state changes. In agreement with the recommendations of the National Institutes of Health,[33] the seizurefree (SF) probability was determined and the overall benefit from surgery was estimated. This was obtained by weighing seizure outcome against the clinically obvious neurological and psychological consequences of surgery. More precisely, the aim of our study was to assess whether a SF condition would fully profit the patient or not.

Method

Sample

One hundred cortical resections were performed from 1980 to 1990. Patients had longterm partial epilepsy which was considered to be intractable after aggressive medical therapy. Fifty nine patients were male, 41 were female, and mean age at operation was 29 years (range 3–59). Mean time between onset of seizures and surgery was 13 years (range 2–40). Forty four patients had symptomatic localisation-related epilepsy in relationship with specific lesions (nine patients had hamartoma; three epidermoid cyst; five astrocytoma; and three focal dysplasia) or history of CNS (nine meningoencephalitis; eight neonatal anoxia; five suffered trauma; and two haemorrhage). Fifty six cases were classified as cryptogenic localisation related epilepsy. Fourteen had presented with febrile convulsions. Histopathological findings are shown in table 1.

Table 1 Histopathological findings according to surgical results with respect to seizures. Specific lesions included nine hamartomas, five astrocytomas, three focal dysplasias and three epidermoid cysts. Aspecific lesions included 25 gliosis and 11 various minor abnormalities

	Seizure free group			Non seizure free group		
	6 months	2 years	4 years	6 months	2 years	4 years
Hippocampal sclerosis	18 (22%)	12 (23%)	7 (27%)	3 (17%)	1 (4%)	
Specific lesions	19 (23%)	12 (23%)	8 (30%)	1 (5%)	3 (12%)	1 (5%)
Aspecific lesions	29 (35%)	16 (30%)	6 (23%)	7 (39%)	11 (46%)	7 (37%)
No abnormality	7 (8%)	7 (13%)	4 (15%)	6 (33%)	6 (25%)	8 (42%)
Insufficient data	9	5	1	1	3	3
Total	82	52	26	18	24	19

Pre-surgical investigations

Clinical features of seizures and the sequence of the ictal symptoms were defined either by direct observation or by EEG or close-circuit TV. Memory functions were explored by the 144 battery Signoret test.[42] The Weschsler Adult Intelligence Scale (WAIS) was used. All patients had CT. Sixty patients had MRI, 45 single photon emission computerised tomography (SPECT-HMPAO), 20 xenon enhanced CT scans (Xe-CT), and one positron emission tomography (PET). For seven patients non-invasive investigations were considered sufficient to locate the epileptic focus. Ninety three patients had chronic stereoelectroencephalography recordings (SEEG). Each flexible electrode had 4–10 stainless steel contacts. Electrodes were implanted under stereotaxic conditions using teleradiography and a Talairach frame.[43] Location and number of electrodes (3–8) were tailored according to the supposed epileptic area. Subdural grid electrodes were used in association with SEEG when explorations of the pre- and postcentral gyri were necessary. Recordings lasted from one to seven days to obtain spontaneous seizures. Intracarotid sodium amytal tests were performed to determine hemispheric language dominance for 12 left handed patients, two right handed patients with early left hemispheric injury, and to assess the risk of an amnesic syndrome in seven cases.

Surgical procedure

Seventy six temporal lobe epileptics had cortical resection ranging from lobectomy (in 50 patients) to amygdalohippocampectomy (23 patients). Resection was limited to the posterolateral temporal cortex in three cases. Frontal lobe epilepsies (23 cases), nine lobectomies and 14 more restricted cortical resections were performed (five in the pre-frontal region; three in the supplementary motor area; three in the premotor area; and three in the orbitofrontal area). One cortical resection concerned the parietal opercular convolutions in the non-dominant hemisphere.

Outcome assessment

Postoperative outcome was prospectively assessed at six months, one year, and thereafter once a year. Operations were carried out from 1980 to 1990, and as a result the patients had different follow up periods. One patient at the first year, two after two years, three at the third and another three after four years, and eight at the fifth year follow up did not participate. The numbers of patients available for follow up were 100 at six months, 93 at one year, 76 at two years, 53 at three years, 45 at four years, and 29 at five years.

All ictal signs including aura were considered as seizures. Possible seizures occurring in the first postoperative month were excluded. Patients were classified at each period of follow up according to two states. The SF state was defined as no seizure in the previous five months at first follow up visit and none in the preceding 12 months at subsequent annual visits. The non seizure free (NSF) state was defined as the occurrence of at least one seizure in the preceding 12 months at subsequent annual visits. Psychiatric symptoms were classified under different mental disorders (major depressive episode, conversion disorder, borderline personality disorder impairment, adjustment disorder with anxious mood or withdrawal, brief reactive psychosis, alcohol abuse) according to the DSM-III-R.[8] Memory functions were tested and visual field defects were explored by Goldman perimetry, but only complaints were taken into account.

Pre- and postoperative interictal signs and symptoms were classified according to their clinical significance: (*a*) mild handicap: symptoms recognisable but no interference with usual life and (*b*) moderate or severe handicap: interference with some or all daily activities. The interictal state was considered more impaired after surgery than before in two situations where either symptoms which were absent before surgery appeared in the postoperative period, involving a moderate or severe handicap, or symptoms which were present before surgery and answerable for a mild or moderate handicap increased to involve a moderate or severe handicap respectively in the postoperative period. Overall surgical benefit was evaluated by considering the interictal consequences of surgery and the benefits of seizure control. Three states were defined as follows: (1) seizure free patients without interictal impairment or presenting no increase in interictal impairment compared with the presurgical period; (2) seizure free patients with more interictal impairment compared with the presurgical period; and (3) non seizure free patients.

Statistical analysis

In the primary data analysis, the cumulative probability of seizure recurrence after surgery was computed using the life table method[19] for the whole sample. The SF probability after temporal lobe and frontal lobe cortical resections were compared using the log-rank test.

The life-table method, however, considers only the first recurrence of seizure(s) and does not account for the possibility that a subject may once again be SF after this recurrence. To allow for such state changes over time, a non-homogeneous Markov chain model was applied.[5] The Markov hypothesis is that the course prediction depends on the present state and not on previous ones. This model makes it possible for the probability computation of a given state at a given period, and the calculation of transitional probabilities between states at a given time. A first analysis was done assuming two states according to seizure relief, that is, SF and NSF as previously defined. SF probabilities from temporal lobe resections were compared with those from frontal lobe resections using the Mantel Haenzel test.[27] A second analysis assessed the overall benefit from surgery making use of the three states defined above. Any agreement between the non-homogenous Markov chain model figures and the data was evaluated by comparing the probabilities given by the model with the percentages actually observed.

Results

Results with respect to seizures

SF probability calculation was different according to the statistical method employed and according to the site of the cortical resection. The actuarial curve (fig 1) indicates a progressive decrease from 82% at six postoperative months to 42% five years after surgery. Using the Markov model (fig 1), the SF probability was 82%, 66%, and 61% at six, 12, and 24 months respectively. After two years the risk of recurrence does not increase since 62% of patients were still supposed SF five years after surgery. The probability of a patient remaining SF at one year was 79% for the SF population at the sixth month. The transitional probability then increases to 96% between the third and the fourth postoperative years. For the NSF subjects at six months, the probability to become SF at one year was 12%. The same probability became 17% between the first and second year, 22% between the second and third year, 11% between the third and fourth year and 8% between the fourth and fifth year.

A significant difference in SF probability existed between temporal and frontal lobe resections to the detriment of the frontal resections whatever statistical method was employed. During the first three postoperative years using the actuarial method (log rank: 4·84; p = 0·03), or for the whole of the follow up period using the Markov model (chi-square from Mantel-Haenzel procedure: 18·2 with 2 degrees of freedom p < 0·001) (fig 2). The SF probability obtained using the Markov chain was 92%, 71%, 69% and 68% for temporal lobe epilepsy, 53%, 50%, 37% and 42% for frontal lobe epilepsy at six months, one year, two years and five years after surgery respectively. For SF patients, the medical treatment was progressively tapered from the second year and, at the fifth post-operative year, 10 out of the 15 SF patients received no antiepileptic drug.

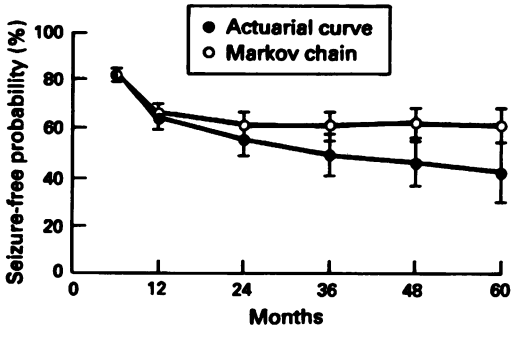

Figure 1 Estimation of the seizure free status from surgery using the Actuarial curve and the Markov chain model.

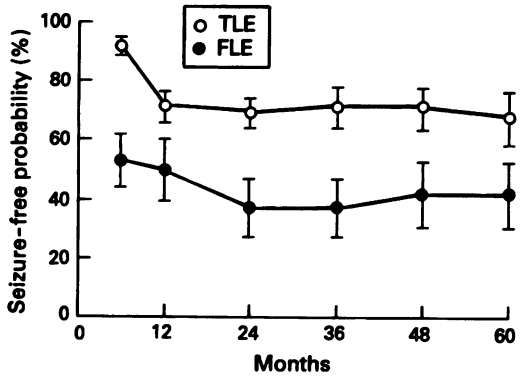

Figure 2 Estimation of the seizure free status from surgery for temporal lobe epilepsy (TLE) versus frontal lobe epilepsy (FLE) using the Markov chain model.

Overall benefit of surgery

The probability, obtained by the Markov chain, of being SF without interictal impairment or, at least, no more interictal impairment compared with the presurgical period (state 1) was 58% at six months, which decreased to 48% during the second year, and then slightly increased to 56% at the fifth postoperative year. The probability of being SF with more interictal impairment compared with the presurgical period (state 2) decreased from 24% at the sixth month to 6% at the fifth year (fig 3). Twenty four, 15, 15, three, three and one patient were classified as state 2 (SF

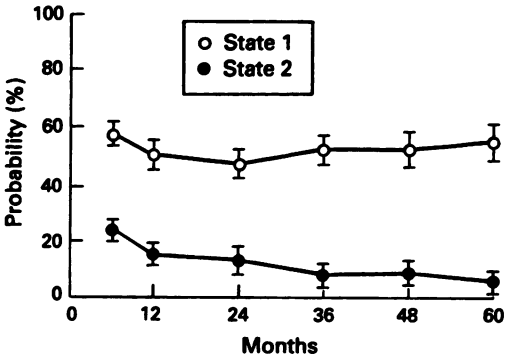

Figure 3 Estimation of the overall benefit from surgery using the Markov chain model. State 1: Seizure free subjects without interictal impairment or with no aggravation in interictal impairment compared with the presurgical period. State 2: Seizure free subjects with aggravation in interictal impairment compared with the presurgical period. (State 3 which represents the non seizure free subjects is not shown).

Table 2 Surgical side-effects involving mild or severe handicap for seizure-free subjects followed

	6 months	1 year	2 years	3 years	4 years	5 years
Seizure free sample total	*82*	*62*	*52*	*31*	*26*	*15*
Major depressive episode	8	3	—	—	—	—
Conversion disorder	2	2	2	1	1	—
Borderline personality disorder impairment	2	1	3	1	1	—
Adjustment disorder with anxious mood	2	1	1	—	—	—
Adjustment disorder with withdrawal	1	1	—	—	—	—
Brief reactive psychosis	—	1	2	—	—	—
Alcohol abuse	—	1	2	—	—	—
Memory complaint	6	3	3	—	—	—
Hemianopia	2	2	2	1	1	1
Frontal syndrome	1	—	—	—	—	—
Total	24 (29%)	15 (24%)	15 (29%)	3 (10%)	3 (11%)	1 (7%)

with more interictal impairment compared to the presurgical period) at six months, one, two, three, four and five years respectively. Surgical side-effects involving SF patients in state 2 are shown in table 2.

Major depressive episodes (eight cases) appeared during the first operative months. Half of them disappeared within the first year, and three within the first two years. In the case of one patient, the follow up period was limited to one year. Other transitory side-effects were adjustment disorders with anxious mood or withdrawal (three patients), brief reactive psychosis (two patients) and frontal syndrome in one patient. Long-lasting side effects were conversion disorders in two patients, half of the memory deficits (3/6) and hemianopia in two patients. Data about borderline personality disorder impairment (three patients) and alcohol abuse (two patients) showed a decrease but the follow up period was restricted.

The values of the probabilities given by the Markov model and the percentages computed from the subjects are shown in table 3. At the sixth month, none was lost from follow up and the probabilities and percentages were the same. The differences are considered to be not significant until the fourth year. At the fifth year, the differences increased with the increased number of patients not being followed up.

Discussion

The prognosis for seizure control after surgery is usually ascertained by averaging data with a variable follow up period duration.[3 6 12 13 22–25 32 39–41 43 49 50] Changes occurring in seizure control during follow up periods have been rarely reported, and with varying conclusions. Falconer[12] stated that long term results were as good as early ones, although a few of the patients who were free of fits during the first year later developed recurrent seizures and conversely, a few of the patients who had occasional seizures in the first year became SF. In another study among patients controlled one year after surgery, 79% were still SF after five years and 63% after 10 years.[11] Among patients who were SF two years after surgery, 81% were controlled at five years, but only 57% at 10 years.[11] The outcome at six months[26] or one year[4] has been considered as an excellent predictor of long term outcome. Different opinions have been expressed. Another study[47] found that >60% of patients who had a total excision of a temporal lobe were seizure free one year after surgery, only 33% remained controlled at five years. Delayed recurrences after a period of 10 years have been observed.[36] Consequently, the assessment of surgery for epilepsy, based upon the average of results arising from a variable follow up period, may be confusing. A better method for the reporting of surgical results would be for all patients to achieve the same follow up period (transversal analysis), for example, one year,[1 10 24] two years,[9] or to wait for a minimum of five years.[2 30] An alternative is a longitudinal survey.[11 47 48]

We chose a longitudinal analysis using a statistical method to take into account both the temporal variability of the seizure-free patients and the variable follow up in a population of patients consecutively operated upon. Such an analysis was possible using the non-homogeneous Markov chain model. The values of the probabilities obtained by this method and the percentages computed from the subjects followed agreed as long as the number lost from follow up was small compared with the population followed up. As the number lost from follow up increased from the last period (the fifth postoperative year), the differences between the values of probabilities and percentages also increased. The SF probability for the whole group suggested by the actuarial curve did not exceed 42% five years after surgery whereas, with the Markov model, 62% were projected to be SF. The differences between

Table 3 Comparison between values of the probabilities given by the Markov chain model and the percentage computed from actual subjects followed

	6 months	1 year	2 years	3 years	4 years	5 years
No of followed patients	100	93	76	53	45	29
Seizure free sample	82 (82%)	62 (66%)	52 (68%)	31 (58%)	26 (57%)	15 (51%)
Seizure free probability	82%	66%	61%	61%	62%	62%
State 1 sample	58 (58%)	47 (50·5%)	37 (48%)	28 (52%)	23 (51%)	14 (48%)
State 1 probability	58%	51%	48%	53%	53%	56%

the results obtained by the Markov model and those obtained by the actuarial curve can be related to the occurrence of isolated seizures or rare seizures in clusters without further relapse, mainly during the first two postoperative years. Engel reported that 38% of patients who experienced many seizures during the first postoperative year were SF for at least two years by the fifth postoperative year.[11] In our study, the transitional probabilities that patients uncontrolled at one year and controlled at two years are 17%, 22% between the second and third year, 11% between the third and fourth year and still 8% between the fourth and fifth year. The transitional probabilities that SF patients will remain so during the period are 83% between one and two years, 87% between two and three years, 96% between three and four years.

Two major determinants of the outcome are the site of the operation and pathology.[3 10 11 40 43] In our study, SF probability from temporal and frontal lobe resections evolved in parallel throughout follow up, obviously to the detriment of frontal lobe resection. At the sixth postoperative month, the SF group was characterised by the prevalence of hippocampal sclerosis and specific lesions (nine patients had hamartomas, five astrocytomas, three focal dysplasias, and two out of the three epidermoid cysts). Absence of neuropathological abnormality in the NSF group was more frequent as the follow up period increased. Aspecific lesions (gliosis and various minor abnormalities) were equally frequent in both groups. Nevertheless, the frequency of this type of lesion decreased with time in the SF group (table 1).

As neurological and mental consequences of cortectomies can modify the interictal state, we tried to evaluate the overall benefit of surgery by balancing seizure relief against possible interictal changes. Only clinically relevant symptoms were taken into account, even if neuropsychological testing often showed subtle variations.[4 34] For example, after ablation of the nondominant lobe, Crandall did not find any handicap affecting the functional capacity of everyday life attributable to these particular cognitive deficits.[4] Among the possible neurological side effects, superior quadrantic visual field defect had no impact on subjective visual perception[20] contrary to more extensive visual defects. Symptoms were therefore classified according to their clinical significance. Symptoms involving moderate or severe handicaps were taken into account. Symptoms involving mild handicaps (those recognisable but not interfering with usual life) were not. In our population, 29%, 24%, 24%, and 28% at six months, one, two, and three years respectively of the SF patients presented with more interical impairment compared with the presurgical period (state 2 sample). The state 2 sample was 9·5% at four years and only one out of 15 patients at the fifth postoperative year.

Major depressive episodes occurred in eight of the 82 SF patients at the beginning of the first postoperative month and none later. These periods all disappeared at the second year. Although interictal mood changes represent the most common psychiatric disorder in epileptic patients, it is mild depression rather than major depressive disorders.[45] This is considered "endogenous" in approximately 40%, but recurrent seizures that bring continued disappointment and persistent social demoralisation are possible contributory factors.[44] The occurrence of a major depressive episode affecting a seizure free patient is all the more unexpected because patients who have been rendered seizure free usually show a reduction in the depression scales.[15 28 38] Nevertheless, James found transient depressions to be not uncommon during a two year period following complete control of seizures[17] and Hermann reported that 18% of one group of patients obtained higher depression scores postoperatively.[15] In another study, 38% of the children who were SF after surgery had difficulty adjusting to a seizure free life and they experienced periods of depression.[31] Interestingly, no change in mood was found in Hermann's patients showing only an improvement in seizure control.[15] As in any chronic disability, epilepsy can become a way of life and when an adult is suddenly freed of it, he or she may find it difficult to adjust at first.

Surgery performed soon after medical intractability has been determined may limit the problems associated with prolonged uncontrolled seizures.[31] Contrary to depression which progressively disappeared, two of our cases of conversion disorder lasted the entire follow up period. In one patient alcohol abuse was observed as well as brief reactive psychotic episodes appearing one year after surgery in one patient and at the second year in another. The development de novo of psychosis following temporal lobectomy despite the postoperative disappearance of seizures, was reported by Jensen and Larsen.[18] The overall incidence of psychological disorders before and after surgical treatment of seizures is roughly equal since abolished psychiatric abnormalities offset developed psychiatric disorders in the postoperative period.[22] Moderate or severe handicap due to memory impairment was noted in six of the 82 SF patients at the sixth postoperative month (7·5%), three of the 62 patients at one year (5%), and three of the 49 at two years (6%). They were among the oldest patients. Memory deficits may be increased after temporal lobectomy and remain so for several years after such operations.[37] Nevertheless, improvement has been also reported.[29] Selective memory deficits are known to be related to the side and extent of resection.[20 29] They are usually of mild importance (symptoms recognisable but not interfering with usual life). There is a risk of global amnesia, however, when the controlateral temporal lobe is dysfunctional either by epileptic discharges (uncontrolled seizures) or by hippocampal damage. In this situation, the risk could be identified by intracarotid amobarbital injection and PET.[37] Other side effects involving a handicap were two permanent hemianopia and one transitory frontal syndrome.

Finally, the probability of obtaining a major

benefit defined as seizure free state without more interictal impairment compared with the preoperative period is, in our population, 56% at the fifth postoperative year. This result is evidence that surgery is an effective treatment for medically intractable epileptic patients more than five times out of 10.

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