Predictive factors of postoperative outcome in the elderly after resective epilepsy surgery

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Highlights

- Epilepsy surgery is a safe and efficient procedure in patients over 50 years
- Advanced age should not limit a potential surgery for drug-resistant epilepsies
- Patients should be carefully selected to prevent neuropsychological or neuropsychiatric complications

ABSTRACT

Objective: To evaluate the efficiency of resective epilepsy surgery (RES) in patients over 50 years and determine prognostic factors.

Results: Over the 147 patients over 50 years (54.9 ± 3.8 years [50-69]) coming from 8 specialized French centres for epilepsy surgery, 72.1%, patients were seizure-free and 91.2% had a good outcome 12 months after RES. Seizure freedom was not associated with the age at surgery or duration of epilepsy. In multivariate analysis, seizure freedom was associated with MRI and neuropathological hippocampal sclerosis (HS) ($p = 0.009$ and $p = 0.028$ respectively), PET hypometabolism ($p = 0.013$), temporal epilepsy ($p = 0.01$). On the contrary, the need for intracranial exploration was associated with a poorer prognosis ($p = 0.001$). Postoperative number of antiepileptic drugs was significantly lower in the seizure-free group ($p = 0.001$). Neurological adverse event rate after surgery was 21.1% and 11.7% of patients had neuropsychological adverse effects overall transient.

Conclusions: RES is effective procedure in the elderly. Even safe it remains at higher risk of complication and population should be carefully selected. Nevertheless, age should not be considered as a limiting factor, especially when good prognostic factors are identified.

Key words: epilepsy surgery, elderly, drug-resistant epilepsy, lobectomy

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INTRODUCTION

Approximately 30% of patients suffering from focal epilepsies would be drug-resistant and candidates for resective epilepsy surgery (RES) [1]. Thus, such a surgery has now been widely accepted as the gold standard treatment for patients with drug-resistant focal epilepsies [2,3]. Nevertheless, despite its effectiveness in obtaining seizure freedom, RES remains underused [4,5]. In addition, it is still commonly thought that surgery in the elderly would not be as efficient as in younger patients and could carry a greater risk of complications [6,7]. This is to compared with the increasing risk of seizures with aging [8].

Thus, the effectiveness and limitations of epilepsy surgery in patients older than 50 years need to be clarified. To date, only few publications have questioned the outcome of surgery in patients older than 50 years [9-15]. In addition these studies mostly focused on temporal lobe epilepsy (TLE) surgery. Results remain contradictory when compared to the younger population [16,17]. Moreover, prognostic factors in this specific population remain largely unclear.

Our aim was to define the efficiency of RES in drug-resistant focal epilepsies in a retrospective multicentre French cohort of patients older than 50 years old. In addition, we analysed predictive factors for being seizure-free, good outcomes (GO) and morbidity.

METHODS

Patients

Data from eight French Epilepsy Departments (Bordeaux University Hospital, Toulouse University Hospital, Marseille APHM, Timone Hospital, Lyon Hospital for Neurology and Neurosurgery, Lille University Hospital, Paris Sainte-Anne Hospital Centre, Paris La Pitié-Salpetrière University Hospital, Rennes University Hospital) were retrospectively analysed. A total of 147 patients over 50 years old who underwent RES for refractory focal epilepsy between 1994 and 2016 were included with a minimum follow-up of one year. All patients underwent clinical assessment, video-electroencephalographic (VEEG) monitoring and brain MRI imaging. All patients gave their written informed consent.

Different data were collected : Preoperative demographic data (age, gender, handedness), history of epilepsy (age at onset, duration of epilepsy, age at surgery, history of febrile seizures, lateralization of epilepsy, history of generalized seizures, seizure frequency before surgery), antiepileptic medications and neuropsychological assessment when available. Typically, IQ, executive functions, memory, language and visiospatiale evaluation were part of the neuropsychological assessment. However, data were not systematically collected nor standardized, especially during late 90's and early 2000's and were not available for every patient. Were also collected:. Invasive and non-invasive presurgical evaluation data (VEEG, stereoelectroencephalographic (SEEG) monitoring, brain MRI, brain positron-emission tomography (PET)); and surgical modalities, types of resection, and post-surgical evolution (postsurgical Engel score, neuropsychological outcome, postoperative impairment, follow-up duration).

Seizure Outcome

Seizure-freedom was defined as Engel score Ia. Good outcome was defined as Engel score I or II [13]. We used a minimum 12-month follow-up as this has been shown to be long enough to establish recurrence of postoperative epilepsy [14]. We divided the patients into two groups: those who were seizure-free since surgery (Engel Ia) and others. We also separated good outcomes (Engel score I or II) and others (Engel score III or IV). We analysed and compared every data set in each group separately.

A surgical complication was defined as any unexpected adverse event other than that which could normally occur following brain surgery. [15]. Complications were defined as minor/transient if they completely resolved within three months after surgery, whereas complications were major if they persisted beyond [16]. When available, neuropsychological outcome was evaluated by neuro-psychological assessment before and after surgery with a minimum of 12 months delay. Decline or improvement of cognitive, memory and behavioural skills were analysed between pre-and post-operative assessments. Patients completed the Wechsler Adult Intelligence Scale. A 20% change in memory scores was defined as clinically relevant [17].

Statistical Analysis

All statistics were performed with SPSS Statistics (IBM V.22). Univariate analysis was performed with Student or Wilcoxon-Mann-Whitney tests. A cut-off of $p < 0.2$ in the univariate analysis was used to enter factors into the multivariate logistic regression analysis. Results were considered statistically significant when the p-value was less than 0.05.

RESULTS

Patient demographic

Of the 147 patients included (77 females), the mean age at epilepsy onset was 20.1 ± 15.5 years (0-67). The mean duration of epilepsy was 34.4 ± 15.5 years (2-59). The mean age at surgery was 54.9 ± 3.8 years (50-69). 56.1% patients underwent right-sided resections. Demographic data and clinical characteristics are summarised in Table 1.

Electrophysiological, Imaging and Neuropathological Examination

Video-EEG demonstrated a strong predominance of temporal onset seizures. SEEG was performed in one quarter of cases and mainly confirmed a temporal epileptogenic zone. All invasive exploration and surgery was decided during local patient's management conference. No adverse event related to SEEG was reported. MRI mainly identified hippocampal sclerosis, focal cortical dysplasia (FCD) (including type IIIa – FCD associated with HS) and benign tumours (including gangliogliomas and DNET). Electrophysiological and imaging data as well as neuropathological examination are summarised in Table 2.

Seizure Outcome

83.7% patients had a good outcome (Engel 1 or 2) including 72.1 percent who were seizure-free (Engel 1a). Figure 1 displays the Engel's score of patients. The mean follow-up was 56.1 months, and 82.5% had at least a 2-year follow-up. In patients older than 60 years, 87.5% had a good outcome and 56.3% were symptom-free. There was no difference between patients between 50 and 60 years old and those over 60 regarding good outcome and seizure freedom ($p = 0.635$ and $p = 0.147$ respectively).

Surgical Data

Most of the patients underwent anterior temporal lobectomy (57%). Regarding the others, mono lobar cortectomy was done in 19%. Other procedures were tailored amygdalo-hippocampectomy (8%), lesionectomy (4%) or complex resection (11%, multi-lobar or multiple procedures, including temporal+insular (75%) or temporal+frontal (25%) – without statistical association with seizure outcome). Good outcome and seizure freedom were significantly higher with temporal lobe resection (TLR) compared to extra-temporal lobe resection (ETLR) ($p <0,001$ and $p = 0,017$ and respectively). Mean number of antiepileptic drugs (AED) was 2.51 before surgery. In the "seizure-free group", mean AED was significantly lower (1.34 vs 2.18, $p = 0.001$). In the good outcome group, it almost reached significance (1.54 vs 2.4, $p = 0.088$).

Neuropsychological Data

Mean Total Intelligence Quotient (TIQ) was 92.5 (62-118 ± 13.38) before surgery and 93.5 (66-106 ± 13.22) after. When compared after and before surgery, 36% of patients had their TIQ worsened, 40%, while were stable and 24% improved. These findings were not correlated with demographic, electrophysiological, imaging nor neuropathological data.

Adverse Events

Neurological adverse events occurred in 21.1% of the patients. They were predominantly ischemic stroke (29%), aphasia (25%), subdural haematoma (16.7%) or infections (8.3%). 50% of side them were characterised as minor. 11.7% of the patients had neuropsychiatric adverse events, which 54.5% were transient. Neuropsychiatric adverse events were mainly characterized by major depression episode (53.3%), confusion (13.3%) or manic episode (13.3%).

Prognostic Factors

Demographic and clinical parameters: We performed univariate analysis to define predictive demographic factors for seizure control after surgery. Two groups were analysed: “good outcome” (Engel score I or II) versus “others” and “seizure-free” (Engel score Ia) and “others”. In univariate analysis, sex, age at surgery, age at epilepsy onset, duration of epilepsy, and other medical history did not influence surgical outcomes. Conclusions were the same for seizure-free patients. Right-sided epilepsy, high seizure frequency and history of febrile seizures were not correlated with a good outcome. Right-sided epilepsy was associated with seizure freedom ($p = 0.026$). Temporal epilepsy was associated with a good outcome ($p = 0.001$). Seizure-free patients had fewer febrile seizures in childhood ($p = 0.004$).

Paraclinical parameters: Presence of MRI lesions was associated with good outcome and seizure freedom ($p = 0.018$ and $p = 0.008$). Subgroups with hippocampal sclerosis, either on brain MRI or neuropathological examination, had a greater likelihood of obtaining seizure freedom (respectively $p = 0.009$ and $p = 0.028$). PET hypometabolism was related to a good outcome ($p < 0.001$) and to seizure freedom ($p = 0.013$). There was a significant difference between non-invasive versus invasive exploration (SEEG) regarding good outcome and seizure freedom ($p = 0.005$ and $p = 0.01$ respectively) with a better outcome when no SEEG was performed.

DISCUSSION

Resective epileptic surgery is effective in patients over 50 years

To date, this is the largest study analysing efficiency of RES in patients over 50 years. Our results show that RES is effective in patients aged over 50 years and can be extended to patients aged over 60 years. More than 90% of patients had a good surgical outcome (ENGEL 1 or 2) and more than 70% became seizure-free (ENGEL 1a). Regarding the patients over 60 years, more than 85% of them had a good outcome and more than 55% were seizure-free.

All together, our results confirm what has been shown in recent studies in older patients, however on a larger multicentric cohort [9,11,12,18]. Depending on the studies, seizure freedom was obtained in 56.3 to 81% of patients. This difference may be due to different aetiologies, type of resection and epilepsy localisation, and various definitions of « seizure freedom » and « good outcome ». In our study, most patients were seizure-free, demonstrating the effectiveness of RES in patients over 50 years. D'Orio et al recently showed similar results with a percentage of seizure freedom (78%) close to what is seen in patients younger than 50 years [18]. This confirms that age should not be considered as a limiting factor.

In addition, RES led to a decrease in AED. The mean number of AED was 2.51 before surgery and 1.56 after, and was significantly lower when seizure freedom was achieved ($p = 0.001$). Interstingly, 16.9% patients completely discontinued their antiepileptic medication. These findings are particularly important in the elderly as side-effects of medications (especially cognitive ones) are common and because of frequent polymedication due to other comorbidities. In addition, AED decrease favour treatment tolerability, adherence and compliance [19] and reduces side-effects and drug interactions, with a positive impact on executive functions [20]. Larger prospective studies will be required to confirm these findings.

Resective Epileptic Surgery Is Safe in patients over 50 years

Neurological adverse effects occurred in only 21.1% of patients, of which 50% were transient. These rates are comparable to those of other studies in the elderly [21,22] but seems to be slightly higher than I what is usually seen in younger patients [18,23]. Nevertheless, caution must be required when comparing the results of studies about epilepsy surgery as there is no well-defined or unanimously accepted definition of what constitutes an adverse event. We tried to use a stricter definition to describe all adverse events after epilepsy surgery that could have increased the postoperative complication rates in comparison to other studies. For instance, we included expected functional results after surgery such as transient motor palsy after supplementary motor area resection, or quadranopsia after posterior temporal resection.

From a neuropsychiatric standpoint, 11.7% of the patients experiment side effects and 54.5% were only transient and mainly in TLE (92.2%). They mostly manifested as postoperative major depression (53.3%), confusion (13.3%) or manic episode (13.3%). Neuropsychiatric outcome are largely unreported in studies about epilepsy surgery thus very limited information is available about the relationship between the two [24,25]. However, our results are concordant with what has been shown in previous studies in older patients [12,26]. Overall, it doesn't seem that epilepsy surgery in the elderly increase the risk of neuropsychiatric complications.

Good outcome after surgery was also associated with stable or improved neuropsychological evaluations ($p = 0{,}004$). However, it should be noted that data were not systematically collected nor standardized, especially during late 90's and early 2000's and were not available for every patient. Nevertheless, our results are very similar to what has been reported in younger adults [27,28]. Nevertheless, the impact of surgery on cognitive functions in the elderly is still a matter of debate. Indeed, several studies reported a negative effect on attentional functioning or memory [15,29], while others showed a comparable cognitive impact in the elderly compared to younger patients [12-14,17]. Interestingly, recent study from Tai et al. reported that cognitive decline after RES is correlated with a possible epilepsy-specific tauopathy in patient over 50 years [30]. Whether this might explain the trend in cognitive dysfunctions in the elderly remain an open question.

Prognostic Factors of Resective Surgery in the Elderly

In this specific population of patients with potential higher risk from surgery, the availability of predictors' outcome could be very helpful for presurgical counselling. Our findings help to establish several prognostic factors of good outcome such as temporal epilepsies, hippocampal sclerosis or PET hypometabolism.

Impact of epileptogenic zone localization: Seizure freedom was significantly higher ($p = 0.026$) in right-sided surgery than in left-sided. This impact of surgery lateralization is probably due to the necessary limitation of any temporal resection due to language considerations in the dominant hemisphere. These is very similar in younger patients surgery [31]. TLE were more likely to have good outcome or obtain seizure freedom after RES than ETLE ($p < 0.001$ in multivariate analysais; table 3). This is concordant with previous studies either in the elderly [32] or the younger population [33]. This difference in outcome might be due to a greater difficulty in identifying the epileptogenic zone, as shown by a greater need for invasive recordings (SEEG) in ETLE ($p = 0.028$). Nevertheless, the percentage of seizure-free patients was 66.7%, proving that RES is still effective in extra-temporal epilepsy.

Impact of imaging findings: Non-lesional MRI was associated with poorer outcomes ($p = 0{,}016$). As in younger patients, this is a major determinant in the postoperative evolution in the elderly [34,35]. On the other hand, hippocampal sclerosis identified on MRI was associated with seizure freedom ($p = 0.009$) and good outcome ($p = 0.028$). This was consistent with pathological findings as pathological HS was associated with GO and SF ($p = 0.006$ and $p = 0.028$ respectively). Finally, PET hypometabolism was associated with good outcomes ($p < 0.001$ multivariate) and seizure freedom ($p = 0.013$ multivariate). PET hypometabolism, especially when it is congruent with MRI lesions and clinical data, but also when MRI is normal, can help in identifying the epileptogenic zone or better define SEEG implantation [36,37].

CONCLUSION

Resective epilepsy surgery in well-selected older adults is an efficient procedure. Even safe it remains affected by a higher risk of complications. Nevertheless, advanced age should not limit a potential surgery for drug-resistant epilepsies. The demographic increase of the older population requires additional studies to better define neuropsychiatric and cognitive outcome in this specific population. Overall, our study, confirms that RES in the elderly provides comparable outcomes to what is known in younger patients. However, it should be borne in mind that it was proposed in a high selected population, which excluded patients who were potentially at risk of complications. Indeed, antecedent occurring mostly in the elderly, such as neurodegenerative disease or increase risk of bleeding, must be carefully investigated. Temporal epilepsies, hippocampal sclerosis or PET hypometabolism were associated with better outcomes. These findings should be confirmed by larger prospective studies and could help in selecting the best candidates for surgery.

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Disclosure of interest

The authors declare no conflict of interest.

Figure 1: Outcome 12 months after surgery evaluated by Engel's score

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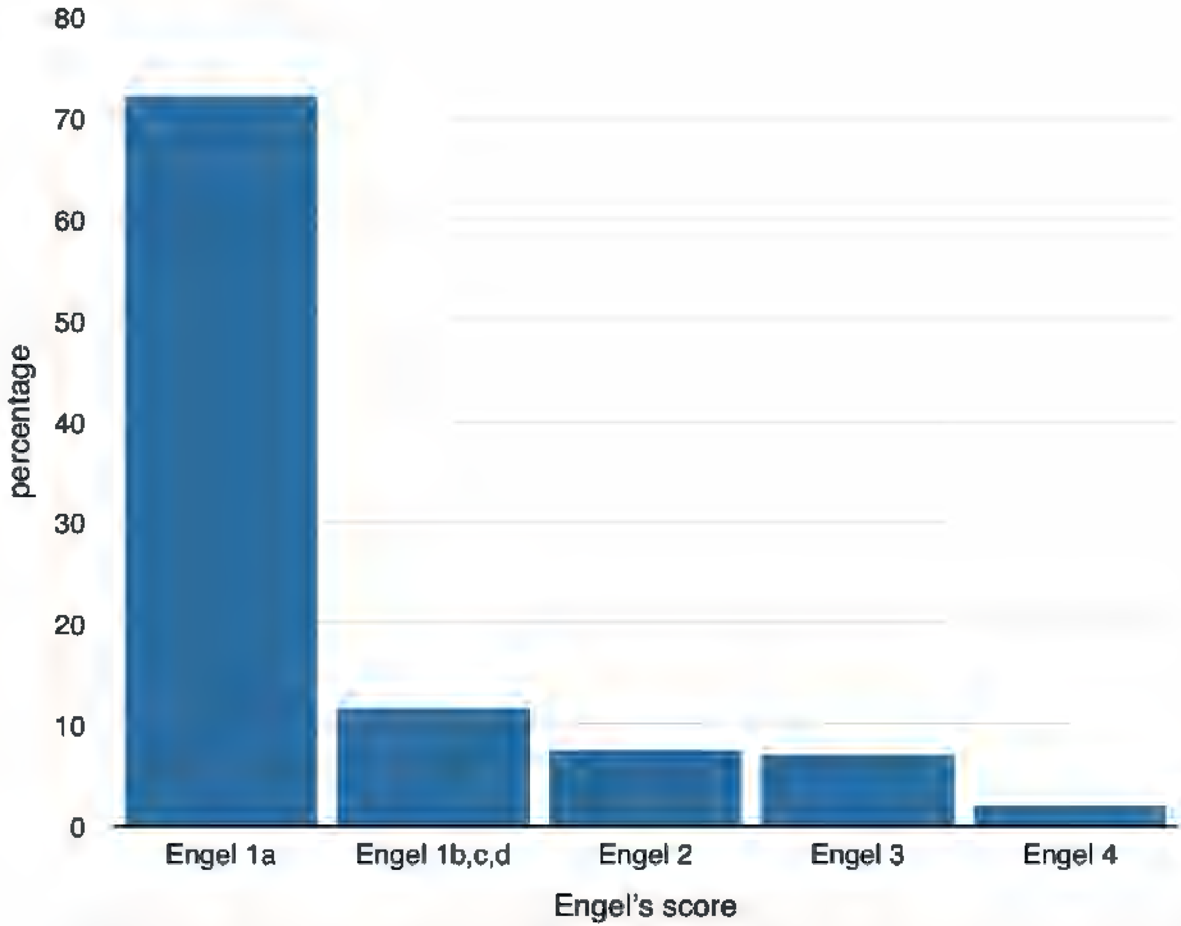

80
70
60
50
40
30
20
10
0
percentage
Engel 1a
Engel 1b,c,d
Engel 2
Engel 3
Engel 4
Engel's score

Table 1 - demographic data

Variables	Values
Age at surgery	54,85 ± 3,84 (50-69)
Gender	
Male n (%)	70 (47,6)
Female n (%)	77 (52,4)
Age at epilepsy onset (years)	20,06 ± 15,5 (0-67)
Duration of epilepsy (years)	34,37 ± 15,5 (2-59)
Lateralization	
Right	56,1 %
Left	43,9 %
Localization	
Temporal	90,2 %
Left-sided	44,7 %
Right-sided	55,3 %
Extratemporal	9,8 %
Left-sided	80 %
Right-sided	20 %
Febrile seizures	28,8 %
Seizures frequency (/month)	9,95 ± 15,74 (0,4-100)
Secondarily generalization	66%
Antiepileptic drugs (n)	
Pre-operatively	2,51 ± 0,87 (1-5)
Post-operatively	1,56 ± 1,07 (0-4)

Variables	**Values**
Video EEG	100%
Temporal	88,6%
Extra-temporal	11,4%
SEEG	25,9%
Temporal	62,5%
Extra-temporal	37,5%
MRI	
Non lesional	5,6%
Isolated hippocampal sclerosis (HS)	58,3%
Focal Cortical Dysplasia (FCD)	10,2%
Cavernomas	9,3%
Focal atrophy	1,9%
Benign tumor	7,4%
DNET	75%
Ganglioglioma	25%
Dysgenesis	0,9%
Unknown	0,9%
Other	5,6%
Neuropathological examination	
Normal	6,3%
Isolated hippocampal sclerosis	52,3%
Focal Cortical Dysplasia (including FCD+HS)	16,2%
Cavernomas	8,1%
Focal atrophy	0,9%
Benign tumor (DNET or Ganglioglioma)	8,1%
Associated lesions (FCD+DNET or focal atrophy+DNET)	0,9%
Dysgenesis	0,9%
Other	6,3%
PET	
Normal	7,1%
Hypometabolism	92,9%
Temporal	64,1%
Multiple	33,3%
Subcortical	2,6%

Table 2 - paraclinic data

Data	**Good outcome (p)**		**Seizure-free (p)**	
	Univariate	**Multivariate**	**Univariate**	**Multivariate**
Normal MRI	**0,018**	0,618	**0,008**	0,418
MRI hippocampal sclerosis	**0,026**	**0,028**	**0,010**	**0,009**
Neuropathological hippocampal sclerosis	**0,013**	**0,006**	**0,002**	**0,028**
Normal neuropathological examination	**0,027**	0,618	**0,003**	0,435
PET abnormality	**< 0,001**	**<0,001**	0,071	**0,013**
Temporal versus extra-temporal epilepsy	**0,039**	<**0,001**	0,63	**0,01**
Isolated temporal surgery = temporal vs extra temp surgery	**0,012**	**0,005**	0,167	**0,05**
Anterior temporal lobectomy	0,137	**0,009**	**0,004**	**0,001**
Right-sided epilepsy	0,084	0,181	**0,026**	0,225
Invasive intracranial exploration (SEEG)	**0,005**	**0,009**	**0,01**	**0,001**
Improvement or stability of the neuropsychological assessment	**0,004**	0,285	0,31	0,166
Postoperative number of antiepileptic drugs	0,063	0,088	**0,003**	**0,001**
Complex febril seizures	0,501	NS	**0,004**	NS (0,601)

Table 3 – Results of the statistical multivariate analysis