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ARTICLE

European trends in epilepsy surgery

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Abstract

Objective

Resective surgery is effective in treating drug-resistant focal epilepsy, but it remains unclear whether improved diagnostics influence postsurgical outcomes. Here, we compared practice and outcomes over 2 periods 15 years apart.

Methods

Sixteen European centers retrospectively identified 2 cohorts of children and adults who underwent epilepsy surgery in the period of 1997 to 1998 (n = 562) or 2012 to 2013 (n = 736). Data collected included patient (sex, age) and disease (duration, localization and diagnosis) characteristics, type of surgery, histopathology, Engel postsurgical outcome, and complications, as well as imaging and electrophysiologic tests performed for each case. Postsurgical outcome predictors were included in a multivariate logistic regression to assess the strength of date of surgery as an independent predictor.

Results

Over time, the number of operated cases per center increased from a median of 31 to 50 per 2-year period ($p = 0.02$). Mean disease duration at surgery decreased by 5.2 years ($p < 0.001$). Overall seizure freedom (Engel class 1) increased from 66.7% to 70.9% (adjusted $p = 0.04$), despite an increase in complex surgeries (extratemporal and/or MRI negative). Surgeries performed during the later period were 1.34 times (adjusted odds ratio; 95% confidence interval 1.02–1.77) more likely to yield a favorable outcome (Engel class I) than earlier surgeries, and improvement was more marked in extratemporal and MRI-negative temporal epilepsy. The rate of persistent neurologic complications remained stable (4.6%–5.3%, $p = 0.7$).

Conclusion

Improvements in European epilepsy surgery over time are modest but significant, including higher surgical volume, shorter disease duration, and improved postsurgical seizure outcomes. Early referral for evaluation is required to continue on this encouraging trend.

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Glossary

ETLE = extratemporal lobectomy; **FDG** = fluorodeoxyglucose; **HS** = hippocampal sclerosis; **SUDEP** = sudden unexpected death in epilepsy; **TLE** = temporal lobectomy.

Comprehensive European epilepsy programs began to emerge in the 1970s that were aimed at achieving tailored epilepsy surgeries.[1] Over the years, this approach has proven highly effective for the treatment of drug-resistant focal epilepsies in children and adults with confirmation by 2 randomized controlled trials.[2,3] Given these results, the American Academy of Neurology issued a recommendation in 2003 advocating lenient early referral to tertiary centers that offer comprehensive evaluation and, if indicated, surgery.[4] To help address the knowledge base of when to refer, the International League Against Epilepsy redefined drug-resistant epilepsy as 2 failed appropriate antiepileptic drug trials.[5] Recent data suggest that earlier surgery leads to better seizure outcome[6–8] and improved quality of life[3] and may mitigate mortality related to sudden unexpected death in epilepsy (SUDEP).[9] However, despite the evidence and official recommendations, observational studies evaluating trends over time reveal that referrals remain delayed[10] and that the number of surgeries is stagnant in the United States[11–13] and individual centers in Germany[14,15] or even decreasing in the United Kingdom,[16] whereas it has been shown to be increasing in children in the Netherlands.[8] This highlights regional differences and potentially different trends in pediatric and adult epilepsy surgery.

Over the last 20 years, there have been major advances in epilepsy knowledge, diagnostic methods, and their application to identify suitable surgical candidates. For example, the spectrum of autoimmune epilepsy has been established[17] that regroups patients who may be poor surgical candidates. On the other hand, patients with MRI-negative epilepsy without an immunologic cause but with a focus well identified on functional imaging (e.g., PET, source imaging) may be better surgical candidates than hitherto suggested.[18] Thus, stronger field MRIs and voxel-based morphometry,[19] molecular[18] and functional imaging,[19] electric or magnetic source localization,[20] and multimodal coregistration[19] may yield improved guidance of surgeries and thus improved outcomes.

Recent meta-analyses report postsurgical seizure freedom rates in the range of 50% to 60%[21,22] but have included operations performed in the 1990s, possibly underestimating the true contemporary surgical outcomes. Single-center studies[8,15] are likely influenced by local policies, available equipment, and referral bias, which could all be attenuated when data are pooled across centers.

The present study included 16 European centers and aimed to determine whether postsurgical seizure outcome has improved in the 21st century, taking into account the evolving practice in the field.[13] As the primary hypotheses, we tested whether recommendations and continuous education have led to earlier referrals and therefore decreased disease duration and whether European epilepsy surgery outcomes have improved in the recent years compared to the 1990s. Secondary outcomes included the total number and types of surgeries, surgical complications ranked by severity, and the number and type of diagnostic tests performed.

Methods

Study design

We designed a retrospective cohort study done in 2 waves with the goal of comparing 2-year epochs 15 years apart (1997–1998 vs 2012–2013 inclusive), hereafter referred to as the 1990s and 2010s, respectively. This delay was chosen because it comprises an era of major technical and knowledge development and the publication of official guidelines but is short enough that each contributing center was able to retrieve detailed information about individual cases. We collected the following primary study outcomes: disease duration from epilepsy onset to surgery (in years) and 2-year postsurgical seizure outcome as the Engel class. We also collected secondary study outcomes: number and type of diagnostic tests performed, number and type of surgeries, number and severity of surgical complications, and the individual center's "surgical ratio" (see below). The target study size was 1,000 patients (500 for each period) to even out the effect of anticipated practice variability across sites and to include enough patients in predefined surgical subgroups.

Epilepsy center inclusion

We invited 27 European epilepsy programs to participate. Inclusion criteria were at least 10 operations per year; surgery on adults, children, or both; access to patient data covering the 2 studied time periods; patients with a follow-up of ≥2 years; and the willingness or possibility to contribute to our study. Sixteen epilepsy centers met the inclusion criteria, including the Swedish National Epilepsy Surgery Register (alphabetically: Bonn, Germany; Brno, Czech Republic; Budapest, Hungary; Geneva, Switzerland; Gent, Belgium; Istanbul, Turkey; Kuopio, Finland; Kork, Germany; London, United Kingdom; Lyon, France; Oslo, Norway; Prague, Czech Republic; Utrecht, the Netherlands; Sofia, Bulgaria; and Vilnius, Lithuania, see also author affiliations for exact center details). Three centers fulfilled inclusion criteria only in the 2010s (Prague, Sofia, Vilnius) because of low surgical volumes in the 1990s but were nevertheless included because staff, monitoring, and imaging equipment were comparable to the other

centers. All centers met regularly at European meetings to exchange views and to discuss clinical cases.

Standard protocol approvals, registrations, and patient consents

Each contributing epilepsy center received approval from an ethical standards committee on human experimentation (institutional or regional) for any experiments using human participants. When indicated by the said committee, each center received written informed consent from all patients (or guardians of patients) participating in the study (consent for research).

Data collection

Data sources included medical records at local hospitals or preexisting site-specific research databases. On the basis of local data, each center filled in a pre-established template spreadsheet including a description of each variable to be collected and coded as numerical values (e.g., 0 = no, 1 = yes). Individual data were systematically checked for any incongruence and validated through clarification with the center of origin before information was merged into 1 common dataset. All cases that did not have follow-up after at least 24 months were discarded (50 [7.8%] and 35 [4.3%] patients in the 1990s and 2010s, respectively). If only a longer outcome was available (e.g., 3 years), then it was assumed that the 2-year outcome was the same. Palliative epilepsy surgeries (resection significantly limited by eloquent cortex, bitemporal epilepsy, or disconnective surgeries, including callosotomies and multiple subpial transections) were excluded from the analysis because they do not aim at seizure freedom (figure e-1, links.lww.com/WNL/A569). Laser thermo-ablation and ablation of hamartomas were not included because they represent categories that were not available in the 1990s. Surgeries for malignant tumor were also not included because they are not considered epilepsy surgery.

Variables

Among descriptive variables, pediatric status was defined as age <16 years at the time of surgery. We collected information on known effect modifiers, including the site of surgery, presurgical diagnosis as defined by MRI (lesional vs MRI negative), and postsurgical histopathology. The site of surgery was divided into temporal lobectomy (TLE; temporal lobe resection of any size, including or excluding mesial structures), extratemporal lobectomy (ETLE; frontal, insular, parietal, or occipital), multilobectomy (>1 lobe, including posterior disconnections), and hemispherectomy (anatomic or functional). Histopathologic categories included hippocampal sclerosis (HS), focal cortical dysplasia (I and II, III if without HS), normal tissue, not available, and other pathology subdivided into benign tumors, gliosis, parenchymal (e.g., polymicrogyria) or vascular malformation, Rasmussen encephalitis, leukomalacia, or dual pathology (defined as HS plus any other MRI epileptogenic lesion for both periods). Missing data on quantitative variables were ignored during the calculation of means and considered a category of their own for histopathology.

The postsurgical seizure outcome was defined according to the Engel classification with additional quantitative criteria for seizure improvement: Engel I (seizure freedom): complete absence of seizures, presence of seizures without impairment of awareness, or seizures of any type limited to the immediate postoperative period or after discontinuation of antiepileptic drugs; and Engel II, III, and IV: almost seizure-free (i.e., ≥90% reduction in seizure frequency), worthwhile improvement (i.e., ≥50% reduction in seizure frequency), and no worthwhile improvement (i.e., <50% reduction in seizure frequency), respectively. Nine cases of death within 2 years of surgery were included as Engel class IV: 6 in the 1990s (2 accidents related to seizures, 1 SUDEP, 1 suicide, and 1 unknown) and 3 in the 2010s (2 SUDEP and 1 perioperative).

Diagnostic tests were coded as binary variables (done/not done) and included invasive EEG, Wada test, neuropsychology, ictal SPECT, interictal fluorodeoxyglucose (FDG)-PET, fMRI (of any modality: language, motor, sensory), and source imaging done with EEG, magnetoencephalography, or combined EEG-fMRI. Invasive EEG, when performed, was subdivided into foramen ovale, subdural grid stereo-EEG electrodes, or a combination.

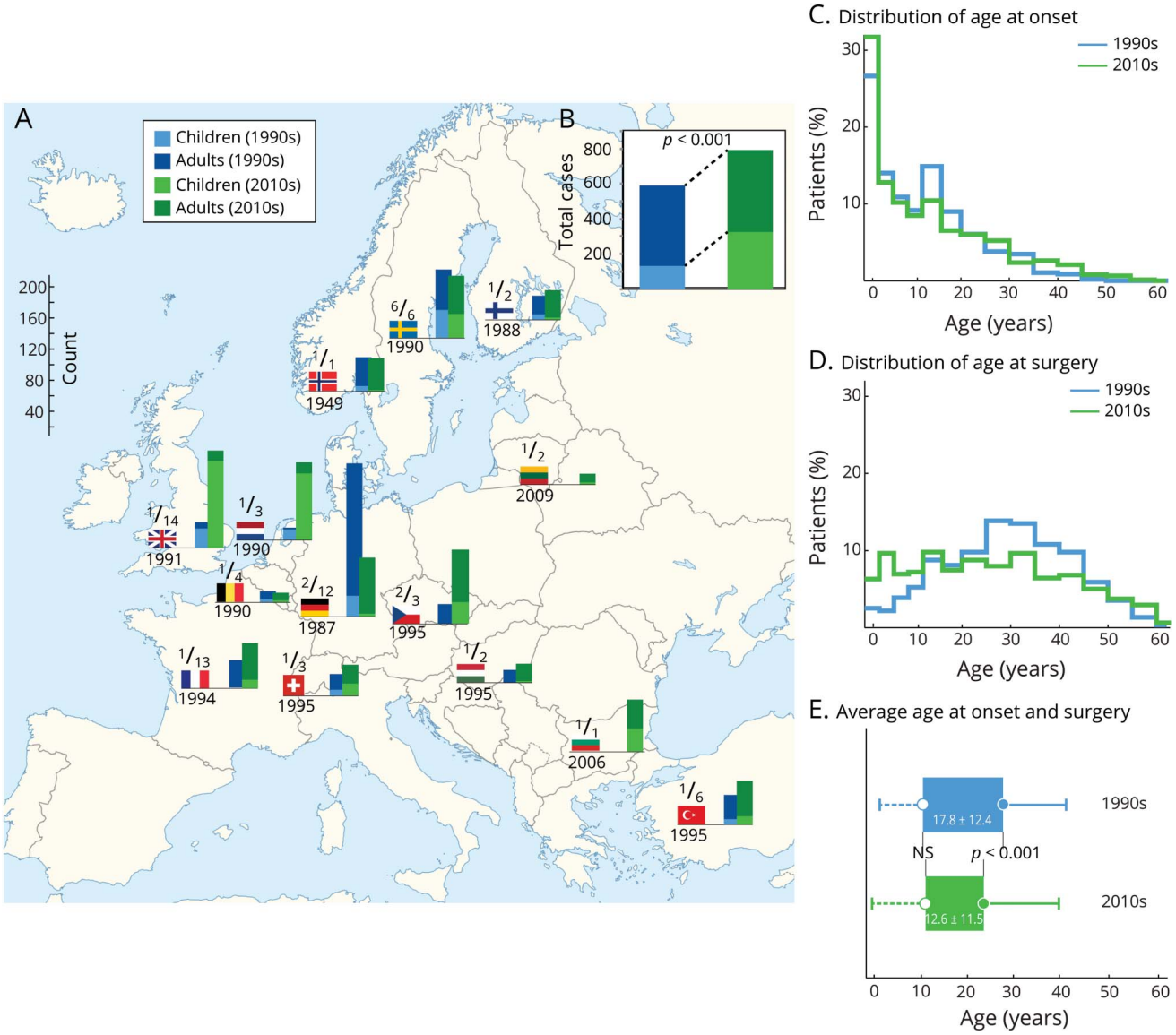
Complications were divided into the following categories inspired from recent work[23]: no complication; transient neurologic (focal deficit of any kind, headaches) or neurosurgical (minor: temporalis muscle atrophy, wound leak, or any intracranial finding that was managed conservatively; major: intracranial or wound infection, intracranial hemorrhages, and hydrocephalus requiring surgery) complications that had completely resolved at the 2-year follow-up; or persistent new or worsened neurologic deficit at the 2-year follow-up (dysarthria, facial paresis, sensory loss, diplopia, behavioral syndrome, any memory deficit, persistent aphasia, hemiparesis, hemianopsia). Quadrantanopia in TLE, visual loss in posterior disconnections, and aggravated hemiparesis in hemispherectomy were considered expected adverse events and therefore not included in complications. Systemic complications were beyond the focus of the present study and therefore not included. The individual center's surgical ratio was defined as the number of surgeries performed over the total number of patients admitted (>3 days) for epilepsy localization over the defined 2-year periods.

Statistics

Unless otherwise specified, continuous variables are presented as mean ± SD and categorical variables as percentage (with corresponding total number). Statistical tests were done with SPSS and Matlab (MathWorks, Natick, MA). We tested the first main hypothesis, decreased disease duration, using a *t* test on the mean. We tested the second main hypothesis, increased seizure freedom, using a multivariate logistic regression model

and presented predictors as odds ratio and 95% confidence interval. The dependent variable was favorable postsurgical seizure outcome (Engel class I), and the main fixed predictor was the period in which the surgery occurred (2010s vs 1990s). We included potential categorical and continuous confounders that were significant on univariate testing with the χ^2 or t test, respectively. We also included known effect modifiers for multivariate statistics (surgery type, lesional vs MRI negative, histopathology). To account for within-center clustering, we used a mixed-effect logistic regression model with the above variables as fixed effects and the individual centers as random effect. The 3 centers that contributed data only for the 2010s were taken into account in the random effect. Among secondary outcomes, we tested the distribution of diagnostic tests, surgery type, and complications using a χ^2 test and the total number of surgeries and the median surgical ratio using a Wilcoxon rank test. The type and number of diagnostic tests were not included as potential confounders of postsurgical outcomes because they specifically contribute to changes in practice over time that was evaluated here.

Figure 1 Changing landscape of European epilepsy surgery over 2 decades



(A) Geographic distribution of all included cases (children and adults) operated on in the 1990s (1997–1998) and 2010s (2012–2013). Above the flag of each country, we indicate a "representativeness index" as the number of included over total number of structured epilepsy surgery programs in the country. Below each flag, we indicate the year when each epilepsy surgery program started systematic recording of its data. Individual centers (n = 16; for visualization, 2 centers merged for Germany and the Czech Republic) showed an increased number of treated cases on average. Note that the number of treated patients decreased in 1 German center because a local health system reorganization between the 2 periods. (B) Total number of cases included in the study. Age categorization reveals an increased proportion of children in the 2010s cohort. (C) Distribution of age at onset of disease was similar during the 2 periods with peaks in infancy and adolescence (3-year steps up to 15 years of age, then 5-year steps). (D) Age at surgery shifted to earlier surgeries in 2010s. (E) Average age at onset (empty circles, SD as dotted line) was not different, but age at surgery (solid circles, SD as solid line) was 5.2 years younger ($p < 0.001$) in the 2010s compared to the 1990s. Disease duration (width of rectangle and numbers therein) was therefore shorter. NS = not significant.

Table 1 Patient and epilepsy characteristics

	1990s	2010s	*p* Value	Missing, %
Total no. of patients	562	736		
Male, % (n)	52.8 (297)	53.8 (396)	0.7	0
Children (age <16 y), % (n)	20.6 (116)	38.7 (285)	<0.001	0.2
Age at onset, y				
Children	3.3 ± 3.7	3.1 ± 3.5	0.5	0.7
Adults	12.4 ± 9.6	16.7 ± 12.1	<0.001	2.3
All	10.5 ± 9.4	11.5 ± 11.8	0.09	2.0
Age at surgery, y				
Children	9.2 ± 4.6	7.7 ± 4.6	0.002	0
Adults	33.2 ± 10.6	34.4 ± 12.4	0.1	0
All	28.3 ± 13.7	24.0 ± 16.4	<0.001	0
Disease duration, y				
Children	5.9 ± 4.2	4.8 ± 3.6	0.005	0.7
Adults	20.9 ± 12.0	17.7 ± 12.0	<0.001	2.3
All	17.8 ± 12.4	12.6 ± 11.5	<0.001	2.0
Excluding 2 centers	18.7 ± 12.5	15.2 ± 12.1	<0.001	2.2
Epilepsy characteristics, % (n)				
MRI negative	13.5 (68)	11.8 (82)	0.4	0
Left lateralization	50.5 (283)	45.1 (332)	0.06	0.2
Localization				
Temporal	76.5 (429)	56.4 (415)	<0.001	0
Multilobar	3.9 (23)	8.3 (61)		
Hemispheric	5.0 (28)	9.2 (68)		
Extratemporal	14.6 (82)	26.1 (192)		
Frontal or insular	9.1 (51)	19.4 (143)		
Parietal	3.0 (17)	4.9 (36)		
Occipital	2.3 (13)	2.0 (15)		
Pathology, % (n)				
Hippocampal Sclerosis	38.7 (217)	19.6 (144)	<0.001	0
Focal Cortical Dysplasia (type I to III)	5.3 (30)	20.0 (147)		
Normal	4.5 (25)	4.4 (32)		
Not available	12.5 (71)	3.9 (29)		
Other	39.0 (204)	52.2 (377)		
Tumor	19.0 (107)	24.0 (176)		
Gliosis	6.2 (35)	8.6 (63)		
Malformation	3.0 (17)	8.1 (60)		
Vascular	3.9 (23)	4.1 (29)		
Dual	0.9 (5)	3.8 (28)		

Continued

Table 1 Patient and epilepsy characteristics *(continued)*

	1990s	2010s	*p* Value	Missing, %
Leukomalacia	1.6 (9)	2.2 (16)		
Rasmussen	1.4 (8)	0.7 (5)		

Disease duration was calculated for all centers and excluding the 2 centers in London and Utrecht because these centers specialized in pediatric epilepsy surgery. Missing values are indicated for each variable. Type III FCD with HS is classified as dual pathology. Malformation included periventricular heterotopia, polymicrogyria, tuberous sclerosis, and megalencephaly.

Data availability

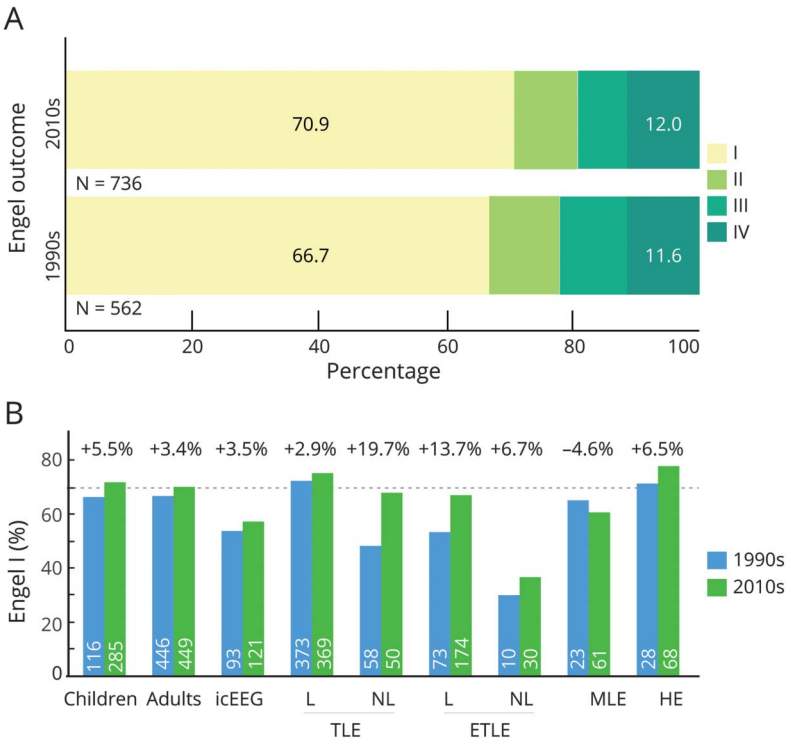
Tabulated and deidentified data can be made available on reasonable request to the corresponding author and after consultation with the other originally contributing authors.

Results

We included 16 individual epilepsy surgery centers that represented a median of 42% of all centers in 14 European countries (range of representativeness index 1/1–1/14, figure 1A). By 1990, the majority of these centers had started structured epilepsy surgery programs with systematic patient registry (median 1993, range 1949–2006). We examined 1,484 epilepsy surgery cases pooled from these centers, retained 1,298 cases meeting our inclusion criteria (see flowchart, figure e-1, links.lww.com/WNL/A569.), and included 1,270 cases (2% missing data) in the main analysis.

The total number of surgeries performed over 2 years increased for individual centers from the 1990s to the 2010s from a median of 31 (range 0–197) to 50 (range 14–125, p = 0.019, Wilcoxon rank test, no missing data, figure 1A). One notable exception is the Bonn center in Germany where the number of surgeries decreased from 183 in the 1990s to 49 in 2010s because of local changes in the health care organization. The estimated surgical ratio (proportion of surgeries per number of inpatient EEG monitoring) remained stable across centers with medians of 26.5% and 24.5%, respectively (p = 0.34, Wilcoxon rank test, missing data for 3 centers). Table 1 summarizes the patients' clinical variables. The proportion of pediatric cases increased from 20.6% to 38.7% (figure 1B). While the distribution of age at disease onset was similar for the 2 periods, showing bimodal peaks in infancy and adolescence (figure 1C), age at surgery peaked in adulthood in the 1990s but shifted to a younger age in the 2010s (figure 1D).

Figure 2 Postsurgical seizure outcome



(A) Percentage of postsurgical Engel classes by decade of surgery. Note a slight expansion of class I in the 2010s. (B) Engel class I outcome in subgroups (absolute numbers in white) shows an overall trend to improvement, except for multilobectomy (MLE). Note marked improvement after nonlesional (NL; or MRI negative) temporal lobectomy (TLE) and lesional (L) extratemporal lobectomy (ETLE). HE = hemispherectomy; icEEG = intracranial EEG.

Table 2 Factors associated with postsurgical Engel class I outcome at 2 years

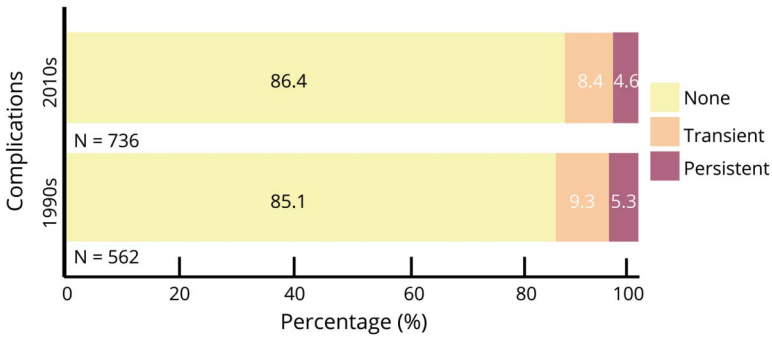
	Engel class I, % (n/N)	Percent change	Multivariate OR (95% CI)	*p* Value
2010s	70.9 (522/736)	4.2	1.34 (1.02–1.77)[a]	0.038
1990s	66.7 (375/562)			
Children	70.4 (283/402)	1.9	1.21 (0.85–1.75)	0.28
Adults	68.5 (614/896)			
Lesional	71.4 (820/1,148)	20.1	1.65 (1.09–2.49)[a]	0.017
MRI negative	51.3 (77/150)			
Surgery type				
Temporal lobectomy	72.2 (609/844)		1 (Referent)	
Extratemporal lobectomy	59.5 (163/274)	−12.7	0.53 (0.37–0.76)[a]	<0.001
Multilobectomy	61.9 (52/84)	−10.3	0.53 (0.31–0.89)[a]	0.016
Hemispherectomy	76.0 (73/96)	3.8	0.92 (0.52–1.62)	0.77
Pathology				
Hippocampal Sclerosis	72.9 (263/361)		1 (Referent)	
Focal cortical dysplasia	62.2 (110/177)	−10.7	0.80 (0.49–1.30)	0.37
Other	71.8 (433/603)	−1.1	1.02 (0.72–1.44)	0.91
Normal	43.9 (25/57)	−29.0	0.51 (0.27–0.97)[a]	0.039
Not available	66.0 (66/100)	−6.9	0.87 (0.51–1.47)	0.6
Disease duration (per year)			1.00 (0.99–1.01)	0.81

Abbreviations: CI = confidence interval; OR = odds ratio.
Note that 1,270 who underwent curative surgery were included for multivariate statistics (2.0% missing due to missing age at disease onset). All are categorical variables except for disease duration.
[a] Independent predictors showing statistically significant OR.

Overall, delay to surgery decreased by 5.2 years from the 1990s to the 2010s ($p < 0.001$, figure 1E and table 1). These effects were driven in part by the 2 pediatric centers, but even when excluding these centers, we found similar age distributions and a significantly decreased delay to surgery of 3.5 years ($p < 0.001$, table 1). Note that some patients with disease onset in childhood are now operated on as children, whereas they would have been operated on as adults in the 1990s. This is reflected in the older age at onset in the adult category. Yet, overall disease duration is shorter across age categories.

Extratemporal surgeries were carried out more frequently over the more recent period. However, the proportion of MRI-negative cases remained stable over time (table 1).

Figure 3 Complication rates and severity by decade of surgery



Note the relative stability of categories over time. Patients are represented only once; therefore, a patient with persistent and other transient complications appears only in the persistent category. See table 3 for type of complications.

Concordant with these observations, a decrease in the number of cases of HS and an increase in focal cortical dysplasia, benign tumors, and dual pathology were noted (table 1).

Figure 2 shows Engel postsurgical seizure outcomes for the 1990s and 2010s. Comparing all curative surgery cases in the 2010s to the 1990s without adjustment identified a trend toward improved Engel seizure outcome after surgery performed in the 2010s ($p = 0.07$, univariate logistic regression, no missing data, figure 2A). Seizure freedom (Engel class I) at 2 years after surgery increased from 66.7% to 70.9%, i.e., a 4.2% difference. The difference became statistically significant when confounders and effect modifiers (e.g., more extratemporal surgeries in 2010s) were included in a multivariate logistic regression model ($p = 0.04$). In the 2010s, the odds of achieving an Engle class I outcome for any curative epilepsy surgery at 2 years was 1.34 higher (95% confidence interval 1.02–1.77, table 2) compared to the 1990s. For both periods, we observed a modifying effect of lesional category (increasing the odds by ≈2), type of surgery (extratemporal and multilobar decreasing the odds by ≈2), and postsurgical normal histopathology (decreasing the odds by ≈2), but there was no additional effect of age at onset, disease duration, or presence of a focal cortical dysplasia. We did not find any significant interaction between the decade and the type of surgery or the age group (adult vs children), suggesting that outcomes modestly improved over time similarly in children and adults and for all types of surgery. Figure 2B shows details of the main effect for surgical subgroups; all, except multilobar resections, showed higher rates of seizure-free patients. The strongest improvements noted in MRI-negative TLE and lesional ETLE likely drove the overall effect.

Table 3 Major and persistent complication rates

	1990s (n = 562), % (n)	2010s (n = 736), % (n)	Percent change, %
Neurosurgical complication			
Intracranial hemorrhage	2.0 (11)	0.7 (5)	−1.3
Intracranial infection	1.1 (6)	0.4 (3)	−0.7
Hydrocephalus	1.1 (6)	1.1 (8)	≈0
Death	0.0 (0)	0.1 (1)	≈0
Persistent neurologic deficit			
Hemiparesis/ monoparesis	1.2 (7)	2.2 (16)	1.0
Aphasia	0.9 (5)	1.1 (8)	≈0
Memory deficit	1.6 (9)	0.5 (4)	−1.1
Behavioral syndrome	0.7 (4)	0.1 (1)	≈0
Hemianopsia	0.5 (3)	0.4 (3)	≈0
Cranial nerve deficit	0.9 (5)	0.1 (1)	−0.8

Number of transient major neurosurgical complications and persistent deficits (a given patient can have >1). Right column shows signed difference from the 1990s to the 2010s approximated by 0 difference when absolute value was <0.7%. No missing data.

Table 4 Use of diagnostic tests, including intracranial EEG

Diagnostic test	1990s (n = 562)	2010s (n = 736)	*p* Value
Tests, n	2.0 ± 1.1	2.2 ± 1.4	<0.001[a]
Neuropsychology, % (n)	87.2 (490)	89.0 (653)	0.32
Source imaging, % (n)	10.9 (61)	28.5 (210)	<0.001[a]
FDG-PET, % (n)	26.6 (149)	39.8 (288)	<0.001[a]
Ictal SPECT, % (n)	15.9 (89)	10.6 (77)	0.006[a]
fMRI, % (n)	0.7 (4)	29.2 (210)	<0.001[a]
Wada, % (n)	31.0 (174)	8.5 (64)	<0.001[a]
icEEG, % (n)	30.8 (173)	29.5 (213)	0.59
Subtype icEEG, n	173	213	
Depth, % (n)	32.4 (56)	46.0 (98)	
Subdural, % (n)	37.6 (65)	34.6 (74)	0.002[a]
Combination, % (n)	22.0 (38)	18.0 (39)	
Foramen ovale, % (n)	8.1 (14)	1.4 (3)	

Abbreviations: FDG-PET = fluorodeoxyglucose PET; icEEG = intracranial EEG. First row shows average total number of test performed per patient ± SD. Other rows show the percentage of patients who had the test. The last 4 rows show the distribution of specific techniques in patients who received intracranial investigations. Structural MRI and EEG monitoring was used for all patients in the 2 decades and are therefore not included. No missing data.
[a] Significant.

Rate and severity of surgical complications were similar in the 1990s and 2010s, despite more complex surgery (e.g., extratemporal, $p = 0.71$, χ^2, missing data for 2 patients, figure 3). Table 3 shows the distribution of specific types of persistent neurologic deficits and transient neurosurgical complications.

As expected, diagnostics evolved over time, and the number of tests per patient increased significantly from 2.0 to 2.2 on average (table 4). Source imaging of spikes (including magnetoencephalography, EEG, and EEG-fMRI) became more prevalent in the 2010s, as did FDG-PET. In contrast, the use of ictal SPECT decreased. The use of the Wada test decreased considerably, the likely result of increased availability of fMRI. The proportion of invasive EEG procedures remained stable; however, the proportion of stereotactic over subdural studies increased in the 2010s. Foramen ovale electrodes were nearly abandoned.

Discussion

Here, we surveyed 16 European tertiary centers that provide epilepsy surgery to a mixed population of pediatric and adult

patients and found that overall postsurgical seizure-freedom improved from 66.7% in the 1990s to 70.9% in the 2010s (+4.2%). This modest improvement is significant only after adjustment for the fact that surgeries performed in the 2010s became more complex (e.g., increased extratemporal procedures). It translates into a number needed to treat of 24 patients to gain 1 Engel class I outcome in the 2010s compared to 1990s. Disease duration decreased by 5.2 years on average, with significant shortening in both children and adults.

Limitations of this study of 2 sequential cohorts in time include its retrospective nature with a potential bias toward random imprecisions for data from the 1990s. The report of complications may be sensitive to better documentation in the 2010s, potentially obscuring a significant improvement in the 2010s compared to the 1990s. Despite a higher inclusion number than targeted, statistical power was lacking for post hoc analysis in surgical subgroups. For this reason, we performed statistical analysis on the overall effect and report illustrative subgroup figures without statistics. Our inclusion criterion for centers with >10 surgeries per year could have obscured possible trends of an increasing number of nonuniversity smaller centers, similar to those observed in nationwide US surveys.[11,12] However, within the European countries included here, the vast majority of epilepsy surgeries are performed at academic centers. Our survey was not inclusive of all European hospitals performing epilepsy surgery but sampled from nationwide systems (Norway, Sweden, pediatric surgeries from the Netherlands), all to one-quarter of the centers in small countries (e.g., Belgium, Lithuania, Switzerland) and down to 1/15 in larger countries like France, and thus, our data are blinded to local transfer or sharing of surgical volume among centers, potentially leading to an underestimation of the actual increase in surgical volume. We chose the 2-year Engel outcome, which may not be definitive but has been shown to be predictive of longer-term seizure outcome (>10 years).[24] Finally, we acknowledge the fact that the pharmacologic arsenal has increased between study periods. However, this is not thought to increase the rate of drug-responsive patients.[25]

Contrary to nationwide UK[16] and US[10–12,26,27] studies and single-center European studies,[8,14,15] our study shows that surgery is probably more widely used and yields improved postoperative seizure control and that presurgery disease duration is shorter. We hypothesize that European practitioners tend to refer potential candidates earlier, likely reflecting official recommendations to curtail years of disabling seizures.[4] Indeed, we observed an important shift from adult to pediatric demography and a decrease in disease duration in both groups. Pediatric programs have largely expanded in Europe[8] and the United States[28] to afford the need to mitigate long-term cognitive disabilities.[29,30] In spite of these encouraging trends, it remains puzzling that in the 21st century the delay from epilepsy onset to surgery still exceeds 10 years on average, in particular in those who undergo surgery in adulthood. Reasons may include temporary seizure remission with new drugs, overestimation of surgical risks, underestimation of seizure-related mortality and morbidity, and lack of access to health care resources.[31] Patients treated by physicians who lack information on the surgical possibility or do not appreciate the potential of a comprehensive evaluation may suffer from delayed referrals. However, the surgical volume in individual centers increased on average, whereas the estimated surgical ratio to total number of admitted patients for epilepsy monitoring remained stable, contrary to US surveys.[11,12] This may indicate more lenient referrals and greater acceptance of epilepsy surgery as a therapeutic option.

Similar to previous observations,[12] the practice of epilepsy surgery has evolved over the decade: we observed a shift to more noninvasive imaging (e.g., FDG-PET) and from invasive functional mapping (Wada test and subdural electrodes) to noninvasive techniques (fMRI). However, the use of invasive brain recordings remained unchanged, encompassing one-third of all cases, with an increasing proportion of stereo-EEG to target deep and extratemporal foci. That said, stereo-EEG was already used in >50% of invasive studies in the 1990s in Europe, sharply contrasting with the more recent spread of the technique in the United States.[32] Regarding the underlying pathologic substrate, resections for HS decreased by half, whereas extratemporal lobe resections for focal cortical dysplasia increased by 4 times in the 2010s.

Overall, the odds of receiving a successful surgery of any type in the 2010s are modestly improved compared to the 1990s.[21] Improvement was most pronounced for surgical subgroups, including MRI-negative TLE (from 48% to 68%, i.e., 20% improvement) and lesional ETLE (from 54% to 68%, i.e., 14% improvement), approaching figures established for more straightforward surgeries such as lesional TLE.[7] This could result from the increased use of multimodal diagnostic tests and the expansion of knowledge of these conditions. For example, delineation of focal cortical dysplasias improves with the use of 3T MRIs with voxel-based morphometry[19] or with MRI-PET coregistration. In addition, the increased use of FDG-PET scans in the 2010s likely identified surgically remediable MRI-negative temporal lobe epilepsy[18] after exclusion of an autoimmune[17] or genetic etiology (e.g., focal-onset seizures in ring chromosome 20 epilepsy[33]). On the other hand, surgical outcomes after lesional TLE were stagnant over time, suggesting that advances in diagnostics or disease understanding were not sufficient for improved surgical success in that category. Given that TLE represents 65% of surgeries across the 2 cohorts, the overall statistical effects reported here were influenced by these stagnant figures.

Despite the advent of noninvasive source imaging,[20] only 3% of our cohort underwent surgery for MRI-negative extratemporal lobe epilepsy, yielding ≈30% to 40% seizure freedom, in agreement with previous studies.[34] This likely reflects a reluctance to attempt surgery in this difficult scenario. Prospective studies may help determine whether consistent and comprehensive application of modern diagnostic techniques could increase surgical success in nonlesional extratemporal lobe epilepsy. Despite increasing surgical complexity, the overall

complication rate remained stable at ≈5%, in line with a recent prospective study[23] and meta-analysis.[35] Of note, our cohort encompassed only 1 perisurgical death but 5 seizure-related deaths in patients who were not seizure-free after surgery, highlighting that the surgical risk has to be balanced with the cumulative lifetime risk of continued seizures.[9]

We strived to pool data from several centers with the aim of obtaining a balanced representation of epilepsy surgery practice in Europe. There are undoubtedly epidemiologic, health system, and medical practice differences within Europe and with other countries. Results presented here remain intimately linked to the practice of individual centers that has evolved over time, possibly at differing paces. However, we believe that the figures shown here reflect knowledge shared and disseminated at national and international conferences, leading to a more harmonized approach in epilepsy care, and may, in that sense, reflect an encouraging global trend to follow guidelines and recommendations. Early referral to specialized centers is crucial to globally reduce years of suffering and unproductivity linked to epilepsy and potentially to improve ultimate cognitive outcomes. As epilepsy knowledge accumulates, current statistics on postsurgical results are required to allow appropriate counseling of prospective surgical candidates. At the turn of the millennium, the postsurgical seizure outcome has improved modestly despite the increasing complexity of procedures and without compromising patient safety. These encouraging trends suggest that future efforts will contribute to optimizing the surgical care of patients with epilepsy.

Author contributions

M.S. and K.P.J.B. designed the study. All authors contributed to data collection. M.O.B., M.S., and T.P. analyzed the data. M.O.B. and M.S. drafted the manuscript. All authors contributed to editing the manuscript.

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