Trends in pediatric epilepsy surgery in Europe between 2008 and 2015: country, center- and age-specific variation

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Key words: epilepsy surgery, children, histopathology, survey, outcome.

SUMMARY

Objective: To profile European trends in paediatric epilepsy surgery (< 16 years of age) between 2008 and 2015.

Methods: We collected information on volumes and types of surgeries, pathologies and seizure outcome from 20 recognized epilepsy-surgery reference centers in 10 European countries.

Results: We analyzed retrospective aggregate data on 1859 operations. The proportion of surgeries significantly increased over time ($p < .0001$). Engel's class I outcome was achieved in 69.3 % of children, with no significant improvement between 2008 and 2015. The proportion of histopathological findings consistent with glial scars significantly increased between age 7 to 16 years old (p for trend= 0.0033), while that of the remaining pathologies did not vary across ages. A significant increase of unilobar extratemporal surgeries (p for trend= 0.0047) and a significant decrease of unilobar temporal surgeries (p for trend= 0.0030) were observed between 2008 and 2015.Conversely, the proportion of multilobar surgeries and unrevealing MRI cases remained unchanged. Invasive investigations significantly increased, especially stereo-EEG. We found different trends comparing centers starting their activity in the 90' to those whose programs were developed in the last decade.

Multivariable analysis revealed a significant variability of the proportion of the different pathologies and surgical approaches across countries, center and age groups between 2008 and 2015.

Significance: Between 2008 and 2015, we observed a significant increase in the volume of paediatric epilepsy surgeries, a stability of the proportion of Engel's class I outcomes and a modest increment in complexity of the procedures.

Key words: epilepsy surgery, children, histopathology, survey, outcome.

INTRODUCTION

Epilepsy surgery is underutilized in both adults[1,2] and children.[3–5] In several previous USA and European surveys[5–13], decreased or stable numbers of resective procedures have been documented in adults, while surgical volumes have steadily grown in paediatric settings. At odds with these findings, a recent European multicenter survey[2] reported an increased utilization of epilepsy surgery in both adults and children, while a single center assessment in Germany[14] described stable volumes of paediatric surgical procedures from 1990 to 2014.

The growing number of paediatric epilepsy surgeries is partly related to the inception and development of new centers dedicated to the treatment of children with drug-resistant seizures[6], with consequent higher awareness of surgery benefits and earlier referral. Broadening of indications (e.g. inclusion of children with epileptic encephalopathies caused by focal/hemispheric lesions), and widespread availability of advanced presurgical diagnostic modalities might also have played a role.[8,10,15,16]

We conducted a survey amongst 20 centers in 10 European countries, in order to profile European trends in paediatric epilepsy surgery between 2008 and 2015 and elucidate factors influencing them. We were specifically interested in analyzing country-specific differences in volumes and types of surgical interventions, pathologies and seizure outcome, in view of the considerable variation in patient care pathways and local facilities for epilepsy surgery across European countries.[2,6,15,17] In addition, considering that the clinical presentation of paediatric candidates for epilepsy surgery is often age-specific,[3] we compared current trends for surgical treatment in two different age-groups, i.e. younger than 7 years old and from 7 to 16 years at surgery. Finally, we compared the surgical activity of centers that started operating on children in the 90' with those that developed their programs in the last decade.

METHODS

We invited 32 European epilepsy surgery centers to participate to the survey through the European Taskforce on Paediatric Epilepsy Surgery (UTASK) and the Commission for Epilepsy Surgery of the Italian League against Epilepsy. Twenty centers (62.5%) from 10

countries were willing to participate. Nine of the 20 centers had started their activity between 1990 and 2000 ('older centers') and the remaining 11 between 2005 and 2008 ('newer centers'). In England, surgical activities have been centralized since 2012.

Each center entered information in the survey that met the following criteria: a) age at surgery 0-16 years; b) intended curative epilepsy surgery between 2008 and 2015 and, c) at least 1-year postoperative follow-up.

We asked retrospective aggregate information per year (between 2008 and 2015) and age group (younger than 7 years and from 7 to 16 years at surgery) as follows: a) total number of surgeries; b) type of surgeries categorized in: unilobar temporal, unilobar extratemporal, multilobar and hemispheric surgeries; c) seizure outcome at last follow-up (Engel's class I [18]); d) pathologies categorized in: glial scars (post-traumatic, post-ischemic[19], etc.), FCD type I, FCD type II, other types of malformations of cortical development (MCD) such as polymicrogyria and heterotopia, tuberous sclerosis, hippocampal sclerosis (associated or not with FCD type IIIa), epileptogenic tumors (associated or not with FCD type IIIb), Rasmussen syndrome, vascular abnormalities (including Sturge-Weber), hypothalamic hamartoma, no lesion i.e. no specific lesion identifiable or characterizable by means of microscopic inspection [19]; e) number of operated patients with unrevealing MRI as diagnosed by the local multidisciplinary team at the time of surgery; f) number and type (Stereo-EEG or subdural electrodes) of extra-operative invasive EEG recordings.

We chose to assess FCD I, FCD II and other MCD separately, owing to the different seizure outcome and level of complexity in presurgical evaluation and surgical approach associated with these pathologies. We did not collect information on HS subtypes.[20]

Each center sent aggregate data to C.B with no indication to individual patients.

The study was given consent by the Paediatric Ethics Committee of Tuscany Region, Italy, and was performed in compliance with the regulations and ethical requirements of each center.

Statistical analysis

We grouped data from participating centers by country and computed a "representativeness index" as the number of included over total number of structured epilepsy surgery centers children were being referred to in each participating country.[2]

According to literature,[2,12,21] we considered as complex procedures: extratemporal surgeries, surgical procedures in patients with unrevealing MRI, and extra-operative invasive EEG recordings.

To assess the number of surgeries, seizure outcome, pathologies and types of surgery per year and country, we performed univariate analyses. Specifically, we computed the proportions of patients in Engel's class I and those of the different pathologies and types of surgeries on the total number of surgeries, per year and country or center group (newer vs older). When appropriate, we calculated the p-value for temporal evolutions trends[22], using the specific STATA 11 routine based on chi square test ('ptrend'; StataCorp, College Station, TX, U.S.A.). The significance level was set at 0.05.

In order to analyze the influence of age on the assessed parameters, we subdivided patients into two groups i.e. younger than 7 years old and aged 7 to 16 years at surgery. We chose this cut-off age, because 7 years old are usually capable of cooperating to active tasks and full neuropsychological assessment[23,24], which may strongly influence the presurgical evaluation.

We performed multivariable analyses by modelling dependent variables (total number of surgical interventions, proportion of Engel's class I, types of surgeries and pathologies) on age group, country or center group (newer vs older) and calendar year at surgery.

We hypothesized that the number of events were distributed in a fixed time-interval, provided that the events occurred randomly, independently in time and at a constant rate. This was an a priori hypothesis, based on the clinical knowledge of the events. In addition, we tested for serial correlation using the Breusch–Godfrey serial correlation LM test (STATA 11) and found no dependence for all outcomes.

We first modeled the above-mentioned dependent variables using the Poisson regression, under the assumption of Over/Under dispersion of the model. We checked this assumption with the evaluation of the Goodness of Fit (GOF). When the assumption of the Poisson regression failed (p for GOF < 0.05), we tested the negative binomial regression. Then, if the GOF did not improve (p<0.05), we chose the model (either Poisson or negative binomial) with the lowest Bayesian information criterion (BIC) and Akaike's information criterion (AIC). GOF and p values are reported for all the models.

The results are presented as incidence-rate ratios (IRR) with 95% confidence intervals. For each independent variable, we chose the reference category in a pragmatic way, i.e. to have a stable group to be compared with the other categories and ensure we could always estimate positive IRR, with no influence on the general configuration of the model or its performance. The significance level was set at 0.05.

In addition, we used the Spearman correlation coefficient (STATA 11, routine 'spearman') to carry out a correlation analysis between Engel's class I outcome and different types of surgeries and pathologies in each age group.

All statistical analyses were performed using STATA 11 (StataCorp, College Station, TX, U.S.A.).

RESULTS

We collected retrospective information on 1859 surgical procedures (Table 1) performed in 799 children aged less than 7 years and in 1060 children aged 7 to 16 years. The "representativeness index" ranged from 1/1 to 1/7

Univariate analysis

Trends for the number of surgeries (Table 1 and S3)

The total number of surgeries increased over time (from 383 in 2008-2009 to 551 in 2014-2015) (p < .0001) in both age groups.

In particular, a significant increase was seen where data from the majority of centers in a country were contributed; Italy (p:0.001), Spain (p:0.001) and the Netherlands (p < .0001).

A significant increase in the number of surgeries had occurred at both older and newer centers (p= 0.008 and p= 0.003, respectively).

Trends for seizure outcome (Table 2 and S3)

Engel's class I outcome was reported in 69.3 % of the patients included in the study (range 53.0-78.8%).

We observed a non-significant increase in the proportion of Engel's class I over time (p for trend for all centers= 0.1031), especially in children aged 7 to 16 years at surgery (p for trend ≥ 7 years at surgery = 0.1573 vs p for trend <7 years=0.3908).

The increase of Engel's class I outcomes did not reach significant values at either newer or older centers.

Trends for pathologies (Figure 1 and Table S1 and S3)

We collected information on pathologies for 1714 out of 1859 (92.2%) surgical interventions. Missing information on histopathology was mainly due to the type of surgery. For instance, hemispheric/multilobar disconnection procedures or the resections were carried out with the intensive use of the ultrasonic aspiration, leading to either no specimens or only a limited amount of often not-representative tissue being available for histological examination.

Epileptogenic tumors (26.9%) and FCD type II (21.4%) were the most frequent pathologies, followed by FCD type I (10.8%) and glial scars (9.2%), with a varied distribution across centers. However, when lumping together FCDI, FCDII and other MCD, the 'MCD/FCD' category was the most represented, followed by epileptogenic tumors (Figure 1 and Table S3).

In addition, tumors and glial scars were more frequent in older than in younger children (31.4 % vs 20.6% and 9.3% vs 9.1%, respectively), while FCDI and FCDII were more frequent in

younger than in older children (12.3% vs 9.7% and 23.7%vs 19.7%, respectively). However, these differences were not significant.

The proportion of glial scars significantly increased from 2008 to 2015 (p for trend= 0.0008). Specifically, this increase was significant in children ≥ 7 years old (p for trend= 0.0033) but not in those < 7 years old (p for trend= 0.0909) and at older centers only (p for trend=0.0025). The proportion of the remaining pathologies remained stable over time at both newer and older centers.

Trends for types of surgery (Figure 2 and Table S2 and S3)

Unilobar extratemporal (ExTLE) surgeries (37.9%) were the most common types of intervention followed by unilobar temporal lobe (TLE) surgeries (30.4%). In addition, unilobar temporal and extratemporal surgeries were more frequent in older than in younger children (36.2% vs 22.7% and 40.8% vs 34.2%, respectively), while hemispheric and multilobar surgeries were more frequent in younger than in older children (40.1% vs 21.1%). However, these differences were not significant.

A significant decrease in the proportion of TLE surgeries (p for trend=0.0047) and a significant increase in the proportion of ExTLE surgeries (p for trend=0.0030) were observed from 2008 to 2015. Specifically, significant figures were found in children ≥ 7 years old (p for trend= 0.0064 for TLE and 0.0112 for ExTLE surgeries) but not in those < 7 years old (p for trend= 0.3050 for TLE and 0.1087 for ExTLE surgeries). The decrease of temporal lobe surgeries from 2008 to 2015 was significant at newer centers (p for trend< 0.0001) but not at older ones (p for trend= 0.528), while the increase of extratemporal lobe surgeries was not significant in either center group (p for trend= 0.050 for older centers vs 0.160 for newer centers).

When considering all centers, the proportion of hemispheric/multilobar surgeries remained stable over time. Conversely, there was a significant increase in the proportion of hemispheric/multilobar surgeries at newer centers only (p for trend=0.0003).

Trends for invasive recordings (Table S4)

Invasive EEG recordings were performed in all centers but five (1 in Romania, 4 in Italy). Specifically, stereo-EEG only was carried out in six centers, subdural electrodes only was used in four centers and either stereo-EEG or subdural electrodes, or both, in five centers. Overall, 373 children (20%) underwent invasive recordings between 2008 and 2015, of whom 99 (26.5%; 52 Stereo-EEG and 47 subdural electrodes) were younger than 7 years of age and 274 (73.5%; 146 stereo-EEG and 128 subdural electrodes) were aged 7 to 16 years.

In addition, 108 children underwent invasive recordings at the newer centers (92 stereo-EEG and 16 subdural electrodes) and 265 (106 stereo-EEG and 159 subdural electrodes) at the older ones from 2008 to 2015. Specifically, stereo-EEG represented 85.2% of invasive recordings performed at newer centers and 40% of those performed at older centers. When newer and older centers were analyzed separately, no significant changes over time were observed for either stereo-EEG or subdural electrodes use.

Trends for operated patients with unrevealing MRI (Table S4)

All centers provided full information on operated patients with unrevealing brain MRI. Overall, 115 children with unrevealing MRI (6.2%) were included in the analysis, of whom 26 (22.6%) aged < 7 years and 89 (77.4%) aged 7 to 16 years.

Children with unrevealing MRI were operated on at five out of 11 (45%) newer centers and seven out of nine (77%) older centers. Thirty-three (28.7%) patients were operated on at newer centers and 82 (71.3%) at older centers. Patients with unrevealing MRI represented 7% of those operated on at newer centers, and 5.9% of those operated on at older centers.

Overall, the proportion of patients with unrevealing MRI operated on per year remained unchanged from 2008 and 2015; however, there was a significant increase of unrevealing MRI at newer centers only (p=0.0077).

Multivariable analysis (Tables 3, 4 and S5)

The number of surgeries significantly increased over time. Specifically, the IRR indicates 33% and 55% increases of the number of surgeries during 2012-2013 (IRR 1.33; CI95% from 1.10 to 1.62) and 2014-2015 (IRR 1.55 CI95% from 1.26 to 1.90) periods compared to the 2008-2009 period, independently from the age at surgery and the center group (newer vs older) (Table 3). In addition, the IRR indicated 30% and 47% increases of the number of surgeries during 2012-2013 (IRR 1.30; CI95% 1.03-1.64) and 2014-2015 (IRR 1.47; CI95% 1.17-1.85) periods compared to the 2008-2009 period, independently from the age at surgery and the country (Table S5).

The total number of surgeries was significantly higher in older children, independently from the calendar year at surgery and the center group (Table 3) and from the country (Table S5) and at older centers, independently from the calendar year and the age group(Table 3).

The proportion of children in Engel's class I did not significantly vary over time, independently from the age and center group (Table 3) and from the country (Table S5).

The proportion temporal lobe surgeries significantly decreased over time, independently from the age and center group (Table 3) and from the country (Table S5) while the proportion of extratemporal lobe surgeries increased over time, independently from the age group and the country (Table S5). The proportion of hemispheric/multilobar surgeries remained unchanged over time (Table 3 and S5).

In addition, the proportion of glial scars significantly increased over time, independently from the age and center group ,while that of the remaining pathologies remained unchanged (Table 4).

Finally, several significant country-, center- (older vs newer) and age-specific differences were observed in the proportion of the different pathologies and types of surgeries (see Table 3 and 4 and S5 for details).

3.5. Invasive recordings (Table 3)

Multivariable analysis revealed significant variations in the number of patients undergoing invasive recordings from 2008 to 2015. Specifically, the IRR indicates 65% decrease in the proportion of subdural electrodes during the 2012-2013 period (IRR 0.65 CI95% from 0.43 to 0.99) periods, compared to the 2008-2009 period, independently from the age and center group. In addition, the IRR indicates 94%, and 99% increases in the proportion of stereo-EEG during the 2010-2011 (IRR 1.94; CI95% from 1.08 to 3.47) and the 2012-2013 (IRR 1.99 CI95% from 1.12 to 3.52) periods, compared to 2008-2009, independently from the age and center group.

The proportion of subdural electrodes was significantly higher and the proportion of stereo-EEG was significantly lower at older vs newer centers.

3.6.Patients with unrevealing brain MRI (Table 3)

The proportion of patients with unrevealing MRI operated on per year remained stable between 2008 and 2015, independently from the age and center group. The proportion of children aged 7 to 16 years with unrevealing MRI was significantly higher compared to younger ages, independently from the calendar year and the center group.

3.7.Comparison of the proportions of Engel's class I, pathologies and types of surgeries between 2008 and 2015 (Figures S1 and S2)

We could not find a statistically significant correlation between seizure outcome and any pathology or type of surgery. However, as illustrated in Figure S1, the proportion of patients in Engel's class I was especially influenced by that of tumors in children younger than 7 years old (direct correlation) and by the proportion of glial scars in children aged 7 to 16 years at surgery (direct correlation). In addition, as shown in Figure S2, the proportion of patients in Engel's class I appeared to be especially influenced by that of hemispheric/multilobar surgeries in children younger than 7 years old (inverse correlation) and by the proportion of unilobar extratemporal surgeries in the 7 - 16 years age group (direct correlation).

DISCUSSION

We profiled the trends of paediatric epilepsy surgery over an 8-year-period in 20 centers from 10 European countries. Collecting data through a European network allowed gathering information from countries with different patient care pathways, healthcare reimbursement systems and local facilities. Likewise, we compared centers starting their activity in the 90' with those that developed their programs in the last decade. Finally, we assessed trends in epilepsy surgery in children younger than 7 years old compared to those aged 7 to 16 years at surgery.

As a main result, we observed a significant increase in the number of surgeries per year using both univariate and multivariable analyses, with higher numbers in older children. These findings are in line with previous nationwide[5,6,8,9] and transnational studies[2] but explanations for the increase in paediatric epilepsy surgery numbers remain ill defined.[5] The advances in structural and functional neuroimaging, EEG monitoring and surgical techniques might have prompted a broader collection of surgical candidates, including some children considered to be inoperable in the past.[3–5] Also, the favorable seizure and developmental outcomes in most children with difficult-to-treat epilepsies, in particular those harboring focal cortical dysplasia and developmental tumors,[2,4,25–27] might have encouraged earlier referral. [2,8,10] In a recent Italian survey,[6] increased surgical referrals in children were mainly attributed to new centers having initiated paediatric epilepsy surgery procedures and the development or expansion of paediatric epilepsy surgery programs in already active centers. In this survey, the increase in the volume of surgeries was significant at both older and newer centers. Opening of new centers and improved dissemination of epilepsy surgery rationale and indications among child neurologists might partly explain the differences we observed between countries. In fact, higher figures were observed in two countries, i.e. Italy, and Spain, where paediatric epilepsy surgery programs started or expanded in the last ten years.[6]

This survey demonstrates a stability of the proportion of Engel's class I outcome over time in multivariable analysis, independently from the country and center group. In addition, no differences were found between older and newer centers. These findings might be due to the

overall steadiness of the proportion of the different types of surgeries and pathologies between 2008 and 2015, even with wide variations across countries and age groups. It might also be related to the fact that all centers involved in the study are considered centers of expertise with a medium to high volume of surgeries per year, regularly participating at the two annual meetings of the U-TASK where strategies for surgically approaching difficult to treat children with epilepsy are discussed and results of pre-surgical evaluations are shared. Only one previous transnational study[2] analyzed changes of seizure outcome in adult and paediatric epilepsy surgery over time and found a limited improvement of seizure outcome between 1997-1998 and 2012-2013. However, a comparison with our study is hampered by considerable differences in inclusion criteria, data collection and methods of analysis.

The increment of extratemporal resections/disconnections and invasive recordings, we observed even in children younger than 7 years of age, can be considered as indices of an increasing complexity of surgical procedures.[28] Nevertheless, the observations that extratemporal procedures mainly increased in older children, while tumors remained more common than other pathologies, and the proportion of surgeries in patients with unrevealing MRI did not significantly change over time when analyzing the total group of centers, might reflect persistent uncertainties affecting early referral of complex cases for paediatric epilepsy surgery.[2,5–7,11] In addition, the decrease of the proportion of temporal lobe surgeries as well the increase of the proportion of MRI-negative cases and hemispheric and multilobar surgeries over time were significant at newer centers only. These findings suggest that newer centers are experiencing an increasing complexity of procedures over time.

The significant decrease of temporal lobe surgeries from 2008 to 2015 demonstrated by univariate and multivariable analyses, is in line with previous studies in adults[1,2,9] and children.[6,10,14] Improved management of complex febrile seizures and febrile status epilepticus, and the lower incidence or improved treatment of brain infections have been considered as possible explanations for reduced antero-mesial temporal surgeries.[12] Owing to our methodology of data collection, we could not assess whether there was a prominent

decrease of HS ILAE type 1[20], which is most often associated with a history of initial precipitating injuries before 5 years of age.[20] However, hippocampal sclerosis accounts for only 5-14% of all pathologies in children with drug-resistant seizures in our own as well in previous studies. [7,8,11]. It has also been hypothesized that the increased number of paediatric surgical procedures might have contributed to the plateauing or even declining number of surgeries in adults.[1,13,21]In line with this observation, the decrease of TLE surgeries we observed in children mainly affected the 7 to 16 years old age group.

We found a significant increase of invasive investigations, with the proportion of subdural electrodes significantly higher and the proportion of stereo-EEG significantly lower at older vs newer centers. However, we observed a non-significant increase in the use of stereo-EEG at older centers. This trend might suggest a shift in preference from subdural electrodes to stereo-EEG at older centers and a high number of stereo-EEG performed at newer centers soon after their inception.

Our findings expand the results of previous nationwide reports,[5–10] and transnational surveys [2,17] in both US and Europe. The consequences of this study are limited by its retrospective nature, the heterogeneity of data and the relatively short observation period. Our conclusions might have been affected by the disparities of the representativeness index between countries and by the lack of information from some major European pediatric epilepsy surgery centers that did not participate to the survey.

In addition, we did not collect information on referral rates to presurgical evaluation at the different centers and, consequently, could not assess whether centers are truly investigating more complex cases, or rather they do but then tend not to operate them.

Despite these limitations, we assessed trends of paediatric epilepsy surgery across Europe between 2008 and 2015, thus revealing country, center- (newer vs older) and age-specific differences in number of surgeries, complexity of procedures and seizure outcome. The good results of epilepsy surgery in most children suggest an overall accurate selection of

candidates, irrespective of disparities in local patient care pathways, healthcare reimbursement systems and local facilities across countries in Europe.

This survey might help understanding strengths and pitfalls of paediatric epilepsy surgery programs European countries and hopefully implement early referral and promote future multicenter prospective studies with long follow-ups.

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DISCLOSURE OF CONFLICTS OF INTEREST

None of the authors has any conflict of interest to disclose.

DATA ACCESSIBILITY STATEMENT

All data relevant to the study are included in the article or uploaded as supplementary information.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

KEY POINT BOX:

- Retrospective aggregate data on 1859 surgical interventions in children were analyzed.
- The proportion of surgeries significantly increased between 2008 and 2015 in Europe, with modest increment of complexity of the procedures.
- Engel's class I outcome was achieved in 69.3 % of children, with no significant increase over time.
- There is significant variability in the proportion of pathologies and surgical approaches across countries, centers and age groups.

REFERENCES

1. Cloppenborg T, May TW, Blümcke I, et al. Trends in epilepsy surgery: stable surgical numbers despite increasing presurgical volumes. J Neurol Neurosurg Psychiatry 2016; 87:1322–9.

2. Baud MO, Perneger T, Rácz A, et al. European trends in epilepsy surgery. Neurology 2018; 91:e96–106.

3. Cross JH, Jayakar P, Nordli D, et al. Proposed criteria for referral and evaluation of children for epilepsy surgery: recommendations of the Subcommission for Pediatric Epilepsy Surgery. Epilepsia 2006; 47:952–9.

4. Ryvlin P, Cross JH, Rheims S. Epilepsy surgery in children and adults. Lancet Neurol 2014; 13:1114–26.

5. Pestana Knight EM, Schiltz NK, Bakaki PM, et al. Increasing utilization of pediatric epilepsy surgery in the United States between 1997 and 2009. Epilepsia 2015; 56:375–81.

6. Barba C, Specchio N, Guerrini R, et al. Increasing volume and complexity of pediatric epilepsy surgery with stable seizure outcome between 2008 and 2014: A nationwide multicenter study. Epilepsy Behav 2017; 75:151–7.

7. Hemb M, Velasco TR, Parnes MS, et al. Improved outcomes in pediatric epilepsy surgery: The UCLA experience, 1986-2008. Neurology 2010; 74:1768–75.

8. Lamberink HJ, Boshuisen K, Van Rijen PC, et al. Changing profiles of pediatric epilepsy surgery candidates over time: A nationwide single-center experience from 1990 to 2011. Epilepsia 2015; 56:717–25.

9. Bui KA, Wahby S, Jetté N, Bouthillier A, Hader WJ KMC and C, collaborators. Inequalities in the utilisation of epilepsy surgery for adults and children in Canada. Epilepsy Res 2018; 148:63-68.

10. Belohlavkova A, Jezdik P, Jahodova A, Kudr M, Benova B, Maulisova A, Liby P, Vaculik M, Lesko R, Kyncl M, Zamecnik J, Tichy M, Komarek V KP. Evolution of pediatric epilepsy surgery program over 2000–2017: Improvement of care? Eur J Paediatr Neurol 2019; 23:456-465.

11. Neligan A, Haliasos N, Pettorini B, et al. A survey of adult and pediatric epilepsy surgery in the United Kingdom. Epilepsia 2013; 54:62–5.

12. Schiltz NK1, Koroukian SM, Lhatoo SD KK. Temporal trends in pre-surgical evaluations and epilepsy surgery in the U.S. from 1998 to 2009. Epilepsy Res 2010; 48:1–6.

13. Englot DJ, Ouyang D, Garcia PA, et al. Epilepsy surgery trends in the United States, 1990-2008. Neurology 2012; 78:1200–6.

14. Cloppenborg T, May TW, Blümcke I, et al. Differences in pediatric and adult epilepsy surgery: A comparison at one center from 1990 to 2014. Epilepsia 2019; 60:233–45.

15. Jayakar P, Gaillard WD, Tripathi M, et al. Diagnostic test utilization in evaluation for resective epilepsy surgery in children. Epilepsia 2014; 55:507–18.

16. Barba C, Mai R, Grisotto L, et al. Unilobar surgery for symptomatic epileptic spasms. Ann Clin Transl Neurol 2016; 19:36–45.

17. Harvey AS, Cross JH, Shinnar S, et al. Defining the spectrum of international practice in pediatric epilepsy surgery patients. Epilepsia 2008; 49:146–55.

18. Engel J. Update on surgical treatment of the epilepsies. Summary of the Second International Palm Desert Conference on the Surgical Treatment of the Epilepsies (1992). Neurology 1993; 43:1612–7.

19. Blumcke I, Spreafico R, Haaker G, et al. Histopathological Findings in Brain Tissue Obtained during Epilepsy Surgery. 2017; 377:1648–56.

20. Blümcke I, Thom M, Aronica E, et al. International consensus classification of hippocampal sclerosis in temporal lobe epilepsy: A Task Force report from the ILAE Commission on Diagnostic Methods. Epilepsia 2013; 54:1315–29.

21. Jehi L, Friedman D, Carlson C, et al. The evolution of epilepsy surgery between 1991 and 2011 in nine major epilepsy centers across the United States, Germany, and Australia. Epilepsia 2015; 56:1526–33.

22. Armitage P. Tests for Linear Trends in Proportions and Frequencies. Biometrics 1955; 11:375–86.

23. Vannest J, Rajagopal A, Cicchino ND, Franks-Henry J, Simpson SM, Lee G A, M, Sroka C HSCAC. Factors determining success of awake and asleep magnetic resonance imaging scans in nonsedated children. Neuropediatrics 2014; 45:370-7.

24. Zilli T, Zanini S, Conte S, et al. Neuropsychological assessment of children with epilepsy and average intelligence using NEPSY II. J Clin Exp Neuropsychol 2015; 37:1036–51.

25. Guerrini R, Duchowny M, Jayakar P, et al. Diagnostic methods and treatment options for focal cortical dysplasia. Epilepsia 2015; 56:1669–86.

26. Giulioni M, Marucci G, Pelliccia V, et al. Epilepsy surgery of “low grade epilepsy associated neuroepithelial tumors”: A retrospective nationwide Italian study. Epilepsia 2017; 58:1832–41.

27. Sibilia V, Barba C, Metitieri T, et al. Cognitive outcome after epilepsy surgery in children: A controlled longitudinal study. Epilepsy Behav 2017; 73:23–30.

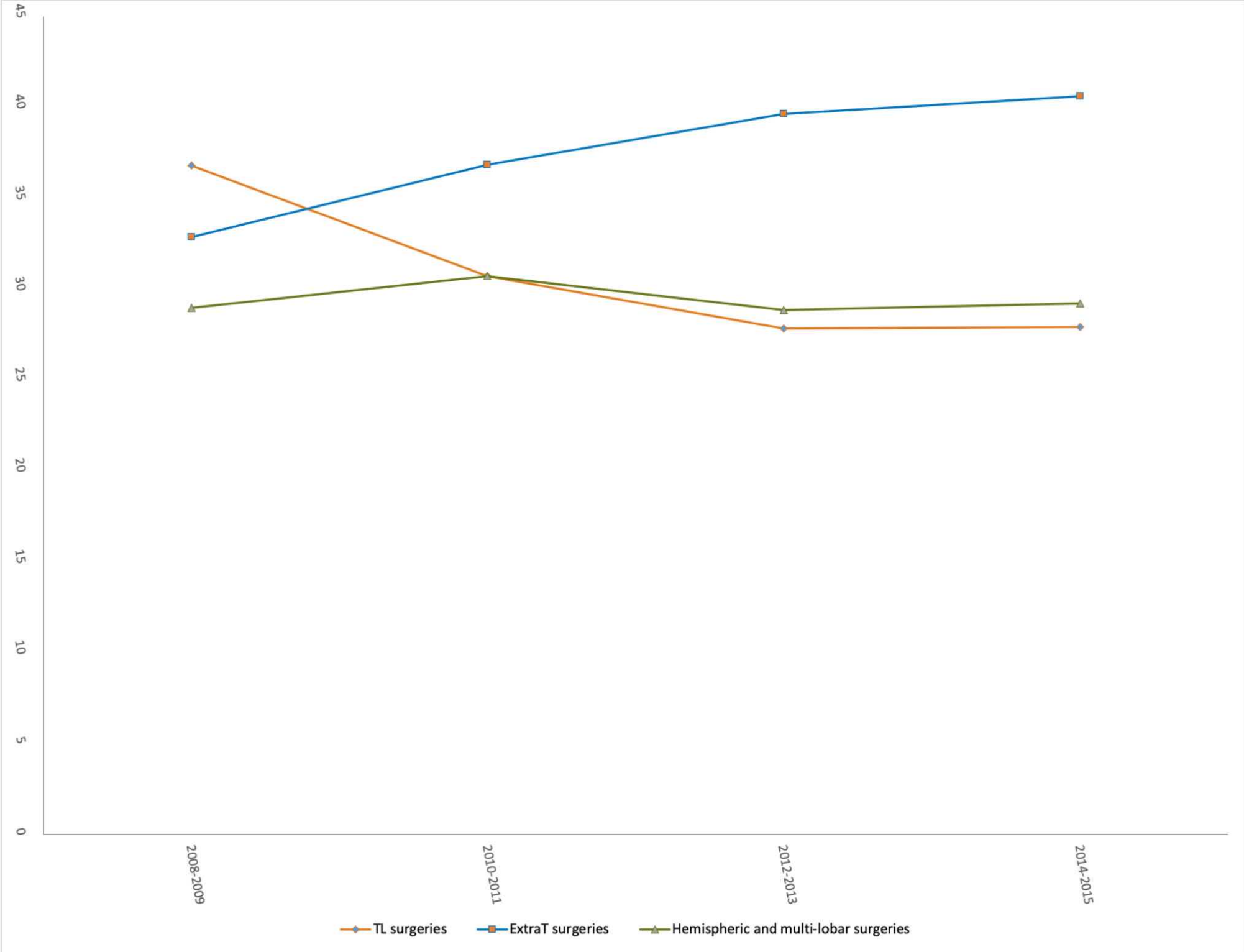
28. Katz JS AT, Katz J. Stereoelectroencephalography Versus Subdural Electrodes for Localization of the Epileptogenic Zone: What Is the Evidence? Neurotherapeutics 2019; 16:59-66.

FIGURE LEGENDS

Figure 1: Trends of the proportion of different pathologies between 2008 and 2015.

Tumors (26.9%) and FCD II (21.4%) were the most frequent pathologies. The proportion of glial scars significantly increased over time (p for trend= 0.0008) while the remaining pathologies were stable between 2008 and 2015. P for trend: Tumors+ FCDIIIb=0.3407; Hippocampal Sclerosis (HS)+FCDIIIa=0.635; Tuberous sclerosis complex=0.511; Vascular abnormalities=0.846; no lesion=0.850; All malformations of cortical development (MCD/FCD)= 0.3285; Hypothalamic hamartoma (HH)=0.147; Rasmussen Syndrome (RS)=0.644.

Figure 2: Trends of the proportions of different types of surgical approaches between 2008 and 2015. Extratemporal surgeries (37.9%) were the most common procedures. A significant increase of unilobar extratemporal surgeries (p for trend= 0.0047) and a significant decrease of unilobar temporal surgeries (p for trend= 0.0030) were observed between 2008 and 2015. Hemispheric and multi-lobar surgeries remained unchanged (p for trend=0.5119).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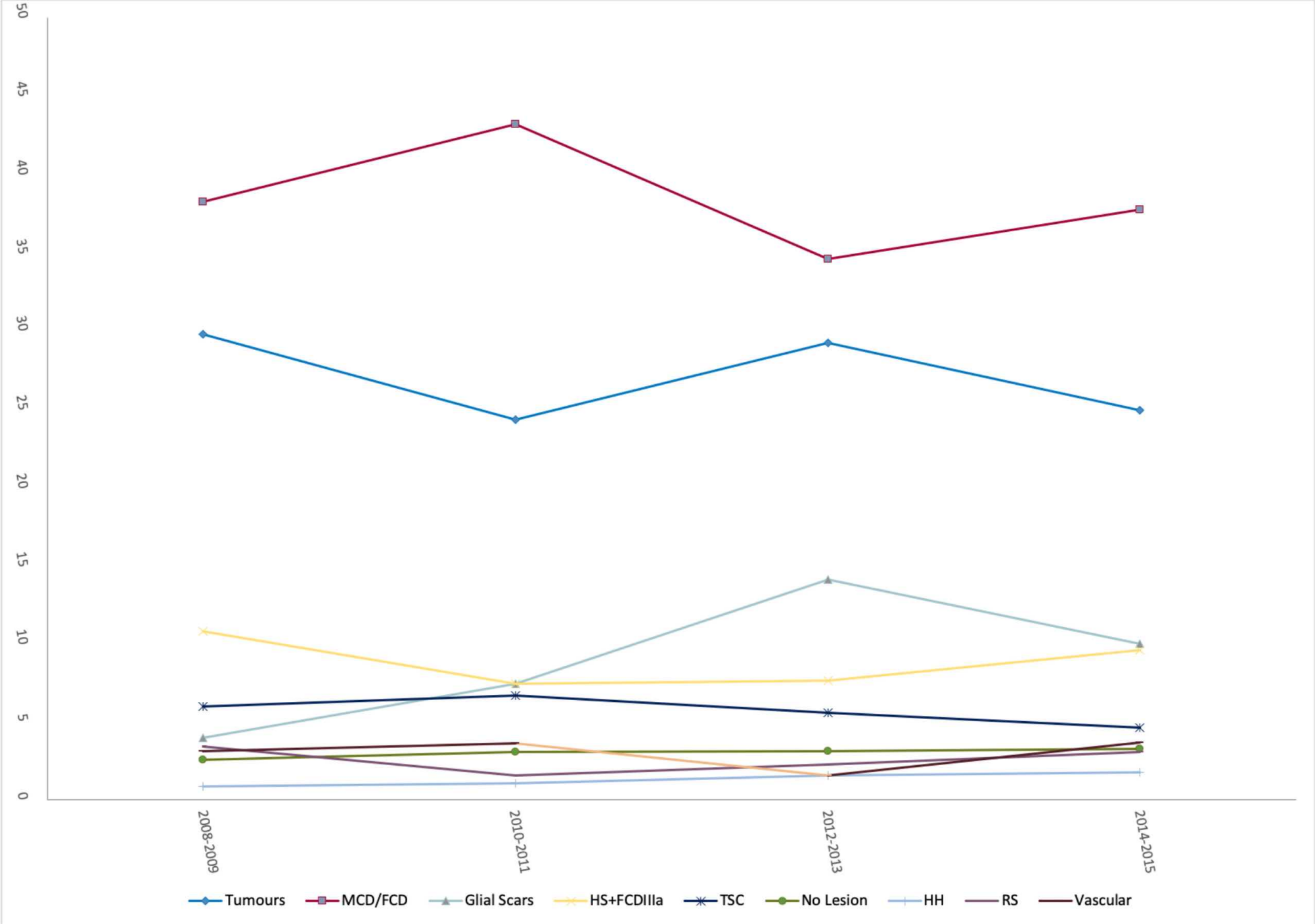
2008-2009
2010-2011
2012-2013
2014-2015
TL surgeries
ExtraT surgeries
Hemispheric and multi-lobar surgeries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2008-2009
2010-2011
2012-2013
2014-2015
Tumours
MCD/FCD
Glial Scars
HS+FCDIIIa
TSC
No Lesion
HH
RS
Vascular

Table 2. Seizure outcome after epilepsy surgeries. Trends over time (2008-2015) at the countries included in the survey

	Bulgaria (1 center)	Finland (1 center)	France (1 center)	Germany (2 centers)	Italy (9 centers)	Portugal (1 center)	Romania (2 centers)	Spain (2 centers)	The Netherlands (1 center*)	England (1 center**)	All Centers
						N (%)					
2008-2009	5/10 (50.0)	23/36 (63.9)	8/15 (53.3)	34/45 (75.6)	89/116 (76.7)	13/22 (59.1)	0/0 (0.0)	13/21 (61.9)	24/34 (70.6)	51/84 (60.7)	260/383 (67.9)
2010-2011	10/18 (55.6)	12/22 (54.5)	16/25 (64.0)	39/51 (76.5)	91/134 (67.9)	12/22 (54.5)	0/0 (0.0)	18/24 (75.0)	40/49 (81.6)	43/81 (53.1)	281/426 (66.0)
2012-2013	9/13 (69.2)	15/30 (50.0)	7/16 (43.8)	41/51 (80.4)	108/134 (80.6)	17/22 (77.3)	1/2 (50.0)	21/37 (56.8)	63/87 (72.4)	62/107 (57.9)	344/499 (68.9)
2014-2015	14/16 (87.5)	15/25 (60.0)	4/10 (40.0)	31/45 (68.9)	134/173 (77.5)	7/11 (63.6)	17/29 (58.6)	36/50 (72.0)	85/99 (85.9)	61/93 (65.6)	404/551 (73.3)
All years	38/57 (66.7)	65/113 (57.5)	35/66 (53.0)	145/192 (75.5)	422/557 (75.8)	49/77 (63.6)	18/31 (58.1)	88/132 (66.7)	212/269 (78.8)	217/365 (59.5)	1289/1859 (69.3)

* on behalf of the Dutch collaborative epilepsy surgery programme

** In England there was a centralization of activities of 4 centers since 2012

Table 1. Total number of epilepsy surgeries. Trends over time (2008-2015) at the countries included in the survey

	Bulgaria (1 center)	Finland (1 center)	France (1 center)	Germany (2 centers)	Italy (9 centers)	Portugal (1 center)	Romania (2 centers)	Spain (2 centers)	The Netherlands (1 center*)	England (1 center**)	All Centers
						N (%)					
2008-2009	10 (17.5)	36 (31.9)	15 (22.7)	45 (23.4)	116 (20.8)	22 (28.6)	0 (0.0)	21 (15.9)	34 (12.6)	84 (23.0)	383 (20.6)
2010-2011	18 (31.6)	22 (19.5)	25 (37.9)	51 (26.6)	134 (24.1)	22 (28.6)	0 (0.0)	24 (18.2)	49 (18.2)	81 (22.2)	426 (22.9)
2012-2013	13 (22.8)	30 (26.5)	16 (24.2)	51 (26.6)	134 (24.1)	22 (28.6)	2 (6.5)	37 (28.0)	87 (32.3)	107 (29.3)	499 (26.8)
2014-2015	16 (28.1)	25 (22.1)	10 (15.2)	45 (23.4)	173 (31.1)	11 (14.3)	29 (93.5)	50 (37.9)	99 (36.8)	93 (25.5)	551 (29.6)
All years	57 (3.1)	113 (6.1)	66 (3.6)	192 (10.3)	557 (30.0)	77 (4.1)	31 (1.7)	132 (7.1)	269 (14.5)	365 (19.6)	1859 (100.0)

* on behalf of the Dutch collaborative epilepsy surgery programme
** In England there was a centralization of activities of 4 centers since 2012