Seizure outcome and drug-freedom related to histopathology up to 5 years after epilepsy surgery: a retrospective, multi-centre, longitudinal, cohort study.

Herm J Lamberink[1a], Willem M Otte[1a,b], Karin Geleijns[1a], Eleonora Aronica[1c,e,f], Roland Coras[2a], Hajo Hamer[2b], Karl Rössler[2c], Christian G. Bien[3a], Thomas Cloppenborg[3a], Alexander Grote[3b,4a], Johannes Schramm[4b], Albert Becker[4c], Christian Elger[4d], John S. Duncan[5a], Jane De Tisi[5a], Maria Thom[5b], Francine Chassoux[6], Bertrand Devaux[6], Georg Dorfmüller[7a], Mathilde Chipaux[7a], Kristina Malmgren[8a,b], Bertil Rydenhag[8a,c], Andreas Schulze-Bonhage[9a], Jürgen Beck[9a], Thomas S. Jacques[10a], J Helen Cross[10b], Cigdem Özkara[11a], Mustafa Uzan[11b], Tom Pieper[12], Manfred Kudernatsch[12], Giancarlo Di Gennaro[13a], Vincenzo Esposito[13a,b], Sylvain Rheims[14a,d], Helene Catenoix[14a,d], Istvan Bodi[15a], Mrinalini Honavar[15a], Petr Marusic[16a], Adam Kalina[16a], Reetta Kälviäinen[17a,b], Leena Jutila[17b], Margitta Seeck[18a], Karl Lothar Schaller[18a], Soheyl Noachtar[19], Katharina Ernst[19], Thomas Grunwald[20], Kristina Koenig[20], Wim Van Paesschen[21a], Johannes van Loon[21b], Tom Theys[21b], Raf Sciot[21c], Armen Melikyan[22a], Lyudmila Shishkina[22b], Martha Feucht[23a], Theresa Scholl[23a], Jose Pimentel[24], Isabel Amorim[24], Tim J. von Oertzen[25a,b], Martin Aichholzer[25b,c], Rita Garbelli[26], Francesco Deleo[26], Felix Rosenow[27a,b], Katja Menzler[27b], Karl Martin Klein[27a,b,d], Pavel Krsek[28], Martin Kudr[28], Olaf Schijns[29a], Jan C. Beckervordersandforth[29b], Victoria San Antonio-Arce[9a,30], Javier Aparicio[30], Alexis Arzimanoglou[30,31], Joseph Toulouse[31], Renzo Guerrini[32a], Carmen Barba[32a], Antonia Jakovcevic[33a], Zeljka Petelin Gadze [33b], Nicola Specchio[34a], Luca De Palma[34a], Savo Raicevic[35a], Dragoslav Sokic[35b,d], Joana Ribeiro[36], Francisco Sales[36], Antonio Gil-Nagel[37], Rafael Toledano Delgado[37], Ingmar Blumcke[2]*, Kees PJ Braun[1a]* on behalf of the European Epilepsy Brain Bank consortium and the European Reference Network "EpiCARE" [§]

*authors contributed equally

Corresponding author: Prof. Ingmar Blümcke, Director, Institute of Neuropathology, University Hospitals Erlangen, Schwabachanlage 6, D – 91054 Erlangen, Germany. T: +49-9131-8526031. E: Ingmar.Bluemcke@uk-erlangen.de

[§] **collaborators of the EEBB consortium:** Floor Jansen[1a], Frans Leijten[1a], Peter van Rijen[1d], Wim G.M. Spliet[1c], Angelika Mühlebner[1e], Burkhard S Kasper[2b], Susanne Fauser[3a], Tilman Polster[3a], Thilo Kalbhenn[3b], Daniel Delev[4a], Andrew McEvoy[5a], Anna Miserocchi[5a], Elisabeth Landré[6], Bares Turak[6], Pascale Varlet[6], Sarah Ferrand-Sorbets[7a], Martine Fohlen[7a], Christine Bulteau[7a,b,c], Anna Edelvik[8], Mukesch Johannes Shah[9a], Christian Scheiwe[9b], Eva Gutierrez Delicado[10b], Martin Tisdall[10b], Christin Eltze[10b], Serdar Akkol[11a] , Kaancan Deniz[11a], Buge Oz[11c], Hans Holthausen[12], Till Hartlieb[12], Martin Staudt[12], Sara Casciato[13a], Pier Paolo Quarato[13a], Felice Giangaspero[13a,c], Nathalie Streichenberger[14b,31], Marc Guenot[14c,31], Jean Isnard[14a], Antonio Valentin[15b], Amanda Chang[15b], Nandini Mullatti[15c], Josef Zamecnik[16b], Jana Zarubova[16a], Martin Tomasek[16a], Arto Immonen[17a], Anni Saarela[17a], Tuomas Rauramaa[17a,b], Johannes Alexander Lobrinus[18b], Kristof Egervari[18c], Shahan Momjian[18a], Elisabeth Hartl[19], Hannah Lohr[19], Judith Kroell[20], Lynn Vermeulen[21a], Evy Cleeren[21a], Pavel Vlasov[22a], Antonia Kozlova[22c], Alexey Vorobyev[22a], Gudrun Goeppel[23a], Sharon Samueli[23a], Thomas

Czech[23b], Johannes Hainfellner[23c], Gertraud Puttinger[25a], Gabriele Schwarz[25a], Harald Stefanits[25b,c], Serge Weis[25d], Roberto Spreafico[26], Flavio Villani[26], Laura Rossini[26], Anke Hermsen[27a], Susanne Knake[27b], Christopher Nimsky[27c], Barbara Carl[27c], Anezka Belohlavkova[28], Barbora Benova[28], Jeroen Bisschop[29a], Albert Colon[29c], Vivianne van Kranen-Mastenbroek[29d], Rob P.W. Rouhl[29c], Govert Hoogland[29a], Jordi Rumiá[30], Alia Ramírez-Camacho[30], Santiago Candela-Cantó[30], Karine Ostrowsky-Coste[31], Eleni Panagiotakaki[31], Alexandra Montavont[31], Pascale Keo Kosal[31], Zeynep Gokce-Samar[31], Clara Milleret[31], Anna Maria Buccoliero[32b], Flavio Giordano[32c], Vlatko Sulentic[33b], Goran Mrak[33c], Andrej Desnica[33c], Giusy Carfi'Pavia[34a], Alessandro De Benedictis[34b], Carlo Efisio Marras[34b], Vladimir Bascarevic[35c,d], Nikola Vojvodic[35b,d], Aleksandar Ristic[35b,d], Olinda Rebelo[36], Angel Aledo-Serrano[37], Irene Garcia-Morales[37], Carla Anciones[37]

Affiliations

[1a] UMC Utrecht Brain Center, Department of (Child) Neurology, University Medical Center Utrecht and Utrecht University, Member of EpiCARE ERN, Utrecht, Netherlands.
[1b] UMC Utrecht Brain Center, Biomedical MR Imaging and Spectroscopy Group, Center for Image Sciences, University Medical Center Utrecht and Utrecht University, Member of EpiCARE ERN, Utrecht, Netherlands.
[1c] UMC Utrecht Brain Center, Department of (Neuro)pathology, University Medical Center Utrecht and Utrecht University, Member of EpiCARE ERN, Utrecht, Netherlands.
[1d] UMC Utrecht Brain Center, Department of Neurosurgery, University Medical Center Utrecht and Utrecht University, Member of EpiCARE ERN, Utrecht, Netherlands.
[1e] Amsterdam UMC, Department of (Neuro) Pathology, University of Amsterdam, Amsterdam, The Netherlands
[1f] Stichting Epilepsie Instellingen Nederland (SEIN), The Netherlands
[2a] Department of Neuropathology, University Hospitals Erlangen, Erlangen, Germany
[2b] Epilepsy Center, University Hospital Erlangen, Germany
[2c] Department of Neurosurgery, University Hospital Erlangen, Germany
[3a] Epilepsy Center Bethel, Krankenhaus Mara, Bielefeld, Germany
[3b] Department of Neurosurgery, Evangelisches Klinikum Bethel, Bielefeld, Germany
[4a] Department of Neurosurgery, University of Bonn Medical Center, Member of EpiCARE ERN, Bonn, Germany
[4b] Professor emeritus, Medical Faculty, University of Bonn, Member of EpiCARE ERN, Bonn, Germany
[4c] Department of Neuropathology, University of Bonn Medical Center, Member of EpiCARE ERN, Bonn, Germany
[4d] Department of Epileptology, University of Bonn Medical Center, Member of EpiCARE ERN, Bonn, Germany
[5a] UCL Queen Square Institute of Neurology Dept of Clinical and Experimental Epilepsy and National Hospital for Neurology and Neurosurgery, Member of EpiCARE ERN, London, UK
[5b] Dept. of Neuropathology, UCL Queen Square Institute of Neurology, University College London, Member of EpiCARE ERN, UK
[6] Hospital Sainte-Anne, GHU-Paris , 75014 Paris, France
[7a] Pediatric Neurosurgery Department, Foundation Rothschild Hospital, Paris, France
[7b] Paris University, MC2Lab, F-92100 Boulogne-Billancourt, France
[7c] Pediatric Neurology Department, Robert Debré Hospital, Paris, France

[8a] Department of Clinical Neuroscience, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Member of EpiCARE ERN, Gothenburg, Sweden
[8b] Department of Neurology, Sahlgrenska University Hospital, Member of EpiCARE ERN, Gothenburg, Sweden
[8c] Department of Neurosurgery, Sahlgrenska University Hospital, Member of EpiCARE ERN, Gothenburg, Sweden
[9a] Epilepsy Centre, University Hospital, Member of EpiCARE ERN, Freiburg, Germany
[9b] Dept. of Neurosurgery, University Hospital, Member of EpiCARE ERN, Freiburg, Germany
[10a] Developmental Biology and Cancer Programme, UCL Great Ormond Street Institute of Child Health and the Department of Histopathology, Great Ormond Street Hospital for Children, Member of EpiCARE ERN, London, United Kingdom
[10b] UCL- NIHR BRC Great Ormond Street Institute of Child Health, Great Ormond Street Hospital for Children, Member of EpiCARE ERN, London & Young Epilepsy, Lingfield, UK
[11a] Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty, Department of Neurology, Istanbul, Turkey
[11b] Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty, Department of Neurosurgery, Istanbul, Turkey
[11c]Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty, Department of Pathology, Istanbul, Turkey
[12a] Neuropediatric Clinic, Epilepsy Centre for Children and Adolescents, Schön Klinik Vogtareuth, Germany
[12b] Paracelus Medical University, Salzburg, Austria
[13a] IRCCS NEUROMED, Pozzilli (IS), Italy
[13b] Department of Neurosurgery, "Sapienza University of Rome", Rome, Italy
[13c] Department of Radiological, Oncological and Anatomo-pathological Sciences, "Sapienza University of Rome", Rome, Italy
[14a] Department of Functional Neurology and Epileptology, Hospices Civils de Lyon and University of Lyon, Member of EpiCARE ERN, Lyon, France
[14b] Centre de Pathologie et Neuropathologie, Hospices Civils de Lyon, Member of EpiCARE ERN, Université Claude Bernard Lyon, Institut NeuroMyogène CNRS UMR 5310 - INSERM U1217, Lyon , France
[14c] Department of Functional Neurosurgery, Hospices Civils de Lyon and University of Lyon, Member of EpiCARE ERN, Lyon, France
[14d] Lyon's Neurosciences Research Center (INSERM U1028 / CNRS UMR5292), Lyon, France
[15a] Department of Clinical Neuropathology, King's College Hospital NHS Foundation Trust, Academic Neuroscience Center, Denmark Hill, King's College Hospital, London SE5 9RS, UK
[15b] Department of Basic and Clinical Neuroscience, IoPPN, King's College London, Academic Neuroscience Center, IoPPN, King's College London, UK
[15c] Department of Clinical Neurophysiology, Kings College Hospital, Denmark Hill, London SE5 5RS, UK
[16a] Department of Neurology, Motol Epilepsy Center, Second Medical Faculty, Charles University, Motol University Hospital, Member of EpiCARE ERN, Prague, Czech Republic
[16b] Dpt. of Pathology and Molecular Medicine, Motol Epilepsy Center, Second Medical Faculty, Charles University, Motol University Hospital, Member of EpiCARE ERN, Prague, Czech Republic
[17a] Kuopio Epilepsy Center, Kuopio University Hospital and University of Eastern Finland, Member of EpiCARE ERN, Kuopio, Finland
[17b] Department of Pathology, Kuopio University Hospital and University of Eastern Finland, Member of EpiCARE ERN, Kuopio, Finland
[18a] Department of Clinical Neurosciences, Geneva, Switzerland
[18b] Department of Pathology and Immunology, Geneva, Switzerland
[18c] Service of Clinical Pathology, Geneva University Hospitals, Geneva, Switzerland

[19] Epilepsy Center, Department of Neurology, Ludwig-Maximilian University Hospital, Munich, Germany
[20] Swiss Epilepsy Center and Dept. of Neurology, University Hospital, Zurich, Switzerland
[21a] University Hospital Leuven, Department of Neurology, Member of EpiCARE ERN, Leuven. Belgium
[21b] University Hospital Leuven, Department of Neurosurgery, Member of EpiCARE ERN, Leuven, Belgium
[21c] University Hospital Leuven, Department of Pathology, Member of EpiCARE ERN, Leuven, Belgium
[22a] Department of Pediatric Neurosurgery, Burdenko National Neurosurgical Center, Moscow, Russian Federation
[22b] Department of Neuropathology, Burdenko National Neurosurgical Center, Moscow, Russian Federation
[22c] Department of Neurophysiology, Burdenko National Neurosurgical Center, Moscow, Russian Federation
[23a] Department of Pediatrics and Adolescent Medicine, Medical University of Vienna, Austria
[23b] Department of Neurosurgery, Medical University of Vienna, Austria
[23c] Institute of Neurology, Medical University of Vienna
[24] Laboratory of Neuropathology, Department of Neurosciences and Mental Health, Department of Neurology, Hospital de Santa Maria (CHULN) , Member of EpiCARE ERN, Lisbon, Portugal
[25a] Department of Neurology I, Neuromed Campus, Kepler Universitätsklinikum, Linz, Austria
[25b] Faculty of Medicine, Johannes Kepler University, Linz, Austria
[25c] Department of Neurosurgery, Neuromed Campus, Kepler Universitätsklinikum, Linz, Austria
[25d] Division of neuropathology, Neuromed Campus, Kepler Universitätsklinikum, Linz, Austria
[26] Epilepsy Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Member of EpiCARE ERN, Milano, Italy
[27a] Epilepsy Center Frankfurt Rhine-Main, Department of Neurology, Goethe University and LOEWE Center for Personalized Translational Epilepsy Research (CePTER), Frankfurt am Main, Germany
[27b] Department of Neurology, Epilepsy Center Hessen, Philipps University, Marburg, Germany
[27c] Department of Neurosurgery, Epilepsy Center Hessen, Philipps University, Marburg, Germany
[27d] Departments of Clinical Neurosciences, Medical Genetics and Community Health Sciences, Hotchkiss Brain Institute & Alberta Children's Hospital Research Institute, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada
[28] Department of Pediatric Neurology, Motol Epilepsy Center, Second Medical Faculty, Charles University, Motol University Hospital, Member of EpiCARE ERN, Prague, Czech Republic
[29a] Department of Neurosurgery, Academic Center for Epileptology, Maastricht University Medical Center, Maastricht, The Netherlands
[29b] Department of Pathology, Maastricht University Medical Center, Maastricht, The Netherlands
[29c] Department of Neurology, Maastricht University Medical Center, and Academic Center for Epileptology Kempenhaeghe/MUMC, Maastricht, The Netherlands
[29d] Department of Clinical Neurophysiology, Maastricht University Medical Center, Maastricht, The Netherlands
[30] Paediatric Epilepsy Unit, Child Neurology Department and Neurosurgery Department, Hospital Sant Joan de Déu, Member of the ERN EpiCARE, Barcelona, Spain
[31] Department of Pediatric Clinical Epileptology, sleep disorders and Functional Neurology; University Hospitals of Lyon (HCL); Member of the European Reference Network EpiCARE, Lyon, France
[32a] Neuroscience Department, Children's Hospital A. Meyer-University of Florence, Member of EpiCARE ERN, Florence, Italy
[32b] Pathology Unit, Children's Hospital A. Meyer-University of Florence, Member of EpiCARE ERN, Florence, Italy
[32c] Neurosurgery Department, Children's Hospital A. Meyer-University of Florence, Member of EpiCARE ERN, Florence, Italy
[33a] Department of Pathology and Cytology, University Hospital Center Zagreb, Affiliated to EpiCARE ERN, Zagreb, Kroatia

[33b] Department of Neurology, University Hospital Center Zagreb, School of Medicine, University of Zagreb, Referral Centre of the Ministry of Health of the Republic of Croatia for Epilepsy, Affiliated to EpiCARE ERN, Zagreb, Croatia
[33c] Department of Neurosurgery, University Hospital Center Zagreb, Affiliated to EpiCARE ERN, Zagreb, Kroatia
[34a] Rare and Complex Epilepsies, Department of Neuroscience and Neurorehabilitation, Bambino Gesu' Children's Hospital, IRCCS, Member of EpiCARE ERN, Rome, Italy
[34b] Neurosurgery Unit, Department of Neuroscience and Neurorehabilitation, Bambino Gesù Children's Hospital, IRCCS, Member of EpiCARE ERN, Roma, Italy
[35a] Laboratory for neuropathology, Department of pathology, Clinical Centre of Serbia, Belgrade, Serbia
[35b] Department for epilepsy, Clinic of neurology, Clinical center of Serbia, Belgrade, Serbia
[35c] Department for functional neurosurgery, Clinic of neurosurgery, Clinical center of Serbia Belgrade, Serbia
[35d] Medical Faculty, University of Belgrade, Serbia
[36] Department of Neurology, Coimbra University Hospital Center, Member of EpiCARE ERN, Coimbra, Portugal
[37] Epilepsy Program, Hospital Ruber Internacional, Madrid, Spain

Abstract

Background: Epilepsy surgery is a widely accepted treatment option for drug-resistant focal epilepsy. A detailed analysis of longitudinal postoperative seizure outcomes and use of antiepileptic drugs across all different brain lesions causing epilepsy is not available. The aim of this study was to provide this information to improve presurgical decision-making and counselling.

Methods: In this retrospective cohort study, patients who had epilepsy surgery between January 1st 2000 and December 31, 2012 at 37 collaborating tertiary referral centres of the European Epilepsy Brain Bank consortium were studied. Included were patients of all ages with histopathology available after epilepsy surgery. Histopathological diagnoses and a minimal dataset of clinical variables were collected from existing local databases and patient records. The primary outcomes were freedom from disabling seizures (Engel class 1/ILAE class 1-2) and medication-freedom at one, two, and five years. Proportions of Engel 1 and medication-free subjects were reported for the eleven main categories of histopathological diagnosis. We studied patterns of seizure outcomes and medication-freedom over time. To control for potential confounding, relative outcomes were computed using random effects multivariable logistic regression and the association between histopathology, duration of epilepsy, age at surgery and outcomes was characterised.

Findings: 9,147 patients were included of whom for 8,191 (90%) seizure outcomes were available at two years, and for 5,577 (61%) at five years. The diagnoses 'low-grade epilepsy associated tumour' (LEAT), vascular malformation, and hippocampal sclerosis had the best seizure outcome, with 78% (1,027/1,325), 74% (328/443), and 72% (2,108/2,948) of subjects being free from disabling seizures at two years after surgery, respectively. The worst seizure outcomes were seen for patients with focal cortical dysplasia type I or mild malformation of cortical development and for those with no histopathological lesion, of whom 50% (213/426) and 54% (396/740) reached Engel 1 at two years respectively. The proportion of patients being both Engel 1 and medication-free was 0–14% at one year and increased to 14–51% at five years. Children were more often drug-free, temporal lobe surgeries had the best seizure outcomes, and a longer duration of epilepsy was associated with reduced chance of favourable seizure outcomes and drug-freedom. This effect of duration was evident for all lesions, except for hippocampal sclerosis.

Interpretation: Histopathological diagnosis, age at surgery and duration of epilepsy are important prognostic factors for outcome of epilepsy surgery. Surgery should be considered in every patient with refractory presumed lesional focal epilepsy.

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Research in context

Evidence before this study. We searched PubMed for original cohort studies describing outcomes of epilepsy surgery related to histopathology or aetiology, using the terms “epilepsy surgery”, “outcome OR seizure”, and “histopathology OR histopathological OR etiology OR aetiology”, without language restriction. Cohorts focusing on specific pathologies or brain regions were excluded since direct comparison of outcomes between pathologies would not be possible, as were studies without a comparison in surgery outcomes between different aetiologies. The search yielded 252 results. Only five identified studies had sample sizes above five hundred patients. The largest cohort sample size was 1,995. None of these studies included all pathological categories, including encephalitis and vascular malformations. Only one study included a category consistent with a brain scar. The only aetiology included in all five studies was hippocampal sclerosis, four looked at either focal cortical dysplasia or the total group of malformations of cortical development, and only three looked at outcomes for tumours. The identified studies did not provide detailed information on expected surgical outcomes for all classes of histopathological diagnoses, nor for specific diagnoses. Postoperative drug-freedom was not reported in any of the studies. None studied the effect of duration of epilepsy in the separate diagnoses.

Added value of this study. This study provides precise epilepsy surgery outcomes up to five years after surgery, for all major classes of histopathological diagnosis and specific sub-diagnoses, based on 9,147 operated patients. For the first time a correlation between long-term seizure- and drug-outcomes and aetiology, age, and epilepsy duration is demonstrated.

Implications of all the available evidence. Epilepsy surgery should be considered in every person with drug-resistant focal and (presumed) lesional epilepsy: surgery renders the majority of selected patients free from disabling seizures. Histopathology is an important determinant of seizure outcome. Other independent determinants of seizure- and drug-outcome are age at surgery, cerebral lobe, and duration of epilepsy. Longer duration of epilepsy is associated with poorer outcome.

Introduction

Epilepsy is one of the most prevalent and severe neurological disorders with around 70 million individuals affected worldwide[1]. Antiepileptic drugs are effective in 70% of patients[2,3], often have side effects[4], and merely suppress seizures, rather than modifying the disease course. Approximately 60% of drug-resistant patients with focal epilepsy have been reported to become seizure free one year after surgery[5] and elective surgery is increasingly recognized as curative treatment option[6]. The range of reported seizure-freedom remains large, however, varying from 15% to 93%, depending – among other factors – on the number of seizures, MRI findings, localization of the epileptogenic zone, need for invasive diagnostics, definition of seizure freedom, duration of follow-up, and underlying pathology[6–10]. Studying postoperative seizure-outcomes in relation to the large spectrum of brain lesions and duration of follow-up, while adjusting for many different determinants of outcome, is a particular challenge and requires large numbers of patients in a multi-center approach. We recently described the spectrum of histopathological diagnoses in 9,523 European patients who underwent epilepsy surgery between 1990 and 2014[5], confirming the unbalanced distribution of various disease conditions, and a large variation in the proportion of histopathological categories between children and adults[5]. Seizure-outcomes were reported for main categories of pathology only at one year after surgery. In the current study, we aimed to substantiate (1) the association between histopathology and seizure outcome and drug-freedom up to five years after epilepsy surgery, and (2) the effects of age at surgery and duration of epilepsy among different histopathological diagnoses on outcome, in a cohort of 9,147 epilepsy surgery patients in Europe.

Methods

Study design and participants

The European Epilepsy Brain Bank is an EU-funded open collaboration of specialised epilepsy centres in 18 countries. Histopathological diagnoses of resected brain tissue were made at the local centres or the German Neuropathology Reference Center for Epilepsy Surgery in Erlangen, Germany[5]. Our study protocol requested all centers to report all consecutive patients undergoing resective epilepsy surgery between January 2000 and December 2012, of whom outcome data was available at 1, 2, or 5 years. All clinical and histopathology data was provided by the centres retrospectively, including sex, age at surgery (children, aged 0-17 years, versus adults), age at onset of epilepsy, duration of epilepsy prior to surgery, lobe of surgery (temporal, frontal, occipital, parietal or multilobar [including hemispheric], and hypothalamic resections), and side of surgery (left, right, and midline, i.e.

hypothalamus). Centres provided seizure outcomes (classified using either Engel or ILAE scores) and antiepileptic drug (AED) use at 1, 2 and 5 years. Patients were included in the study when seizure outcome was available for at least one of these time-points. In case of multiple surgeries, only histopathology and outcome data related to the first surgery were included. Histopathological diagnoses were divided into eleven main categories, see Appendix page 2 for details.

The study was approved by the ethics review board of the University of Erlangen, and all procedures were conducted in accordance with the ethics requirements of the contributing centres. Written informed consent was not required in this retrospective cohort study and all patient data processed anonymously. Seizure outcome data of some patients who were included in single-centre cohort studies have been reported before[11–15].

Outcomes

Individual surgery outcomes were "freedom from disabling seizures" and "both freedom from disabling seizures and drug-freedom". From submitted data, freedom from disabling seizures was defined as Engel class 1 (including subtypes 1a-1d)[16] or ILAE class 1 and 2[17], for at least one year at time of outcome determination. Drug-freedom was defined as complete freedom from AEDs.

Statistical analysis

Absolute numbers of patients free from disabling seizures and AED-free patients are presented with proportions and corresponding 95% confidence interval (CI). The difference in Engel 1 scores between one and five years after surgery was computed in the subgroup of patients with complete information at both time points. The association between histopathology and Engel 1 at two years was determined with random-effects logistic regression models. We characterised the association between drug-freedom and histopathological diagnosis only at five years, because the proportion of drug-free patients increases with the number of years after surgery. Models were corrected for age at surgery, year of surgery, location of surgery, duration of epilepsy, and account for possible interaction effects between duration, age at surgery and the eleven main histopathology categories. Heterogeneity between centres was modelled through random intercepts.

Missing data were imputed by means of multiple imputations using chained equations with predictive mean matching[18], with twenty imputation sets[19]. Imputed dataset regression results were pooled according to the Rubin rule. Uncertainty intervals were computed using 500 bootstrapped model fits, taking the 0.025^{th} and 0.975^{th} percentiles. The age of onset of hippocampal sclerosis patients below the age of 6 was set to missing, as was their duration of epilepsy, which were

subsequently imputed. This was done because descriptive analyses revealed that in 35% (1,048/3,038) of hippocampal sclerosis cases, collaborators had indicated an age of seizure onset below 6 years, therefore hampering a certain differentiation between a noted age of precipitating febrile seizures or status epilepticus (typically occurring before 6 years of age) and the age of onset of the subsequent temporal lobe seizures. Statistical modelling was done with 'glmmTMB' and 'lme4' version 0.2.2.0 and R, version 3.4.1.

Role of the funding source

No funding source had any role in study design, collection, analysis and interpretation of data, writing the report, or the decision to submit the paper for publication.

Results

Information regarding histopathological diagnosis was available for 9,601 epilepsy surgeries from 37 centres. Re-operations (77 subjects) and patients without clinical follow-up (377 subjects) were excluded, leaving a total cohort of 9,147 patients of whom 5,462 (73%) had an age at onset of epilepsy < 18 years, and 2,952 (33%) were below the age of 18 years at time of surgery. Age at surgery ranged between <1 and 75 years, 48% were female, and 66% of surgeries were in the temporal lobe (Table 1). The largest categories of histopathological diagnosis were hippocampal sclerosis (36%), LEAT (16%), and FCD II (10%) (Table 1). Demographics regarding the age at onset, duration of epilepsy, age at surgery and the anatomic location of surgery varied across the different histopathological diagnoses (Table 1).

Table 1 | Demographics

						Location of surgery (%)				
Diagnosis	**N**	**% Female**	**Age at onset**	**Duration**	**Age at surgery**	**T**	**F**	**P**	**O**	**other**
Hippocampal sclerosis	3260	54	14 (10-22)	18 (10-28)	35 (25-44)	98	0	0	0	2
LEAT	1493	43	11 (5-18)	7 (3-16)	21 (13-34)	74	12	5	3	5
FCD II	884	49	3 (1-7)	9 (4-17)	14 (6-26)	20	50	6	5	17
No lesion	836	44	11 (4-18)	12 (6-23)	28 (16-40)	62	15	4	3	15
Vascular malformation	494	46	19 (9-32)	7 (3-17)	33 (19-46)	61	16	5	4	14
FCD I/mMCD	471	54	5 (1-13)	7 (4-15)	16 (7-29)	44	29	3	4	19

MCD-other	459	47	1 (0-3)	6 (2-14)	8 (3-20)	19	17	4	3	56
FCD-NOS	450	45	4 (1-9)	10 (4-21)	18 (8-32)	33	38	7	4	16
Non LEAT	356	44	16 (9-32)	5 (2-13)	29 (17-41)	56	22	6	4	11
Scar	298	37	6 (1-14)	9 (4-16)	18 (9-34)	28	18	3	8	43
Encephalitis	146	50	6 (3-14)	5 (2-9)	13 (8-24)	26	18	1	1	52
Total	9147	48	10 (3-18)	11 (4-21)	27 (14-39)	66	15	3	2	13

Legend to Table 1: For every histopathological diagnosis, the median (interquartile range) age at onset of epilepsy, age at surgery, and duration of epilepsy are given, as well as the percentage of temporal (T), frontal (F), parietal (P), occipital (O), and midline/multilobar/hemispheric-other surgeries. FCD = focal cortical dysplasia. MCD = malformation of cortical development. mMCD = mild MCD. NOS = not otherwise specified. LEAT = low-grade epilepsy associated neuro-epithelial tumour.

Of all variables relevant to the analyses, 15% of data points were missing (21,380/146,352), mainly in the AED status at five (59%), two (40%) and one year (36%), the seizure outcome at five (39%), two (10%), and one year (10%), and the age at onset of epilepsy (18%) and duration of epilepsy (18%) (Appendix page 3).

Freedom from disabling seizures and AED-freedom over time

The histopathological diagnosis with most favourable seizure outcome at two years was 'LEAT' with 78% (1,027/1,325) Engel 1 patients at two years, followed by 74% (328/443) in vascular malformations, 72% (2,108/2,948) in hippocampal sclerosis, 70% (288/413) in FCD-NOS, 68% (212/310) in non-LEAT, 65% (517/796) in FCD II, 60% (74/124) in encephalitis, 59% (155/261) in glial scar, 54% (396/740) in patients with no histopathological lesion, 52% (212/405) in MCD-other. Fifty percent (213/426) of patients with FCD I or mMCD were free from disabling seizures at two years. Outcome varied considerably between diagnostic subcategories (Table 2, Appendix page 4).

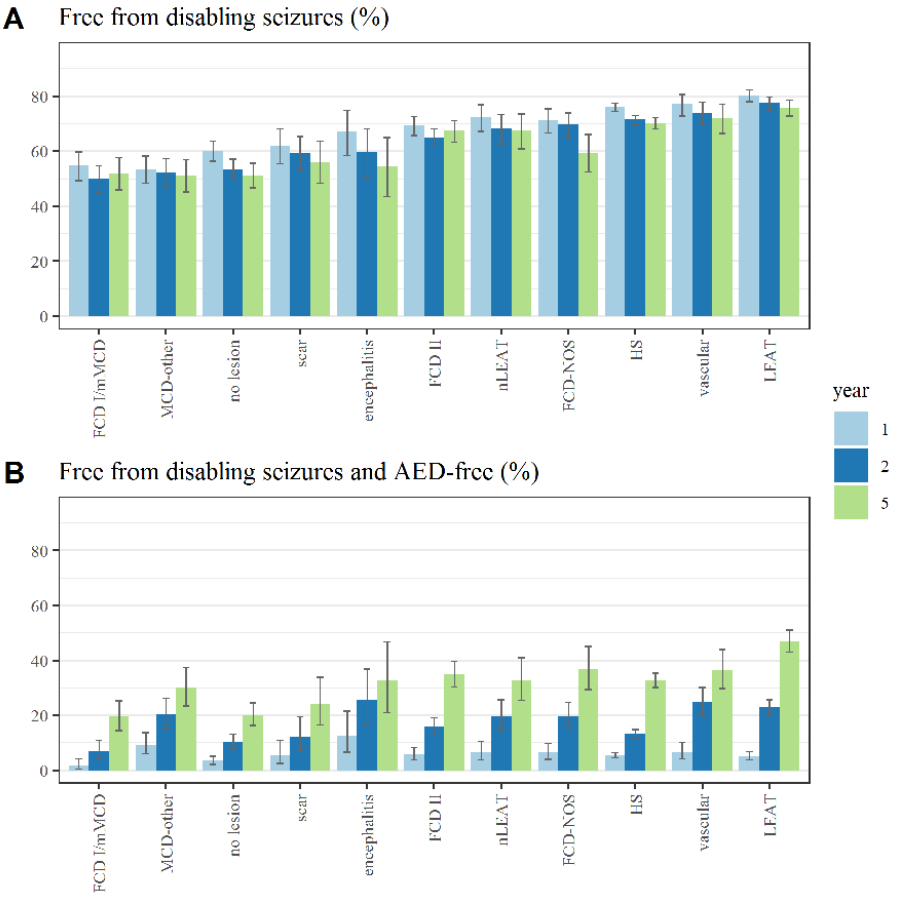
Table 2 | Freedom from disabling seizures (Engel 1/ILAE 1-2) at 1, 2 and 5 years after surgery by histopathological diagnosis.

Histopathological diagnosis	1 year (n = 8247)	2 years (n = 8191)	5 years (n = 5577)
Hippocampal sclerosis	76% (74-78; 2359/3103)	71·5% (70-73; 2108/2948)	70·3% (68-72; 1471/2092)
LEAT	80·3% (78-82; 1063/1323)	77·5% (75-80; 1027/1325)	75·9% (73-79; 681/897)

	LGNET	71·6% (60-81; 58/81)	70·6% (61-79; 72/102)	68·9% (57-79; 51/74)
	DNET	77·7% (74-81; 390/502)	74·8% (71-79; 362/484)	74·6% (70-79; 256/343)
	ganglioglioma	83·1% (80-86; 557/670)	80·4% (77-83; 540/672)	77·4% (73-81; 336/434)
	LEAT-other	82·9% (72-90; 58/70)	79·1% (67-88; 53/67)	82·6% (68-92; 38/46)
FCD II		69·4% (66-73; 496/715)	64·9% (62-68; 517/796)	67·4% (63-71; 370/549)
No lesion		60·2% (56-64; 435/723)	53·5% (50-57; 396/740)	51·2% (47-56; 247/482)
	gliosis	60·3% (56-64; 330/547)	53·2% (49-57; 311/585)	51·1% (46-56; 182/356)
	normal tissue	59·7% (52-67; 105/176)	54·8% (47-63; 85/155)	51·6% (43-61; 65/126)
Vascular malformation		77·1% (73-81; 357/463)	74% (70-78; 328/443)	72·2% (67-77; 205/284)
	vascular-other	72·5% (63-80; 87/120)	65·8% (57-74; 79/120)	61·6% (50-72; 53/86)
	cavernoma	78·7% (74-83; 270/343)	77·1% (72-81; 249/323)	76·8% (70-82; 152/198)
FCD I/mMCD		54·7% (49-60; 198/362)	50% (45-55; 213/426)	51·9% (46-58; 153/295)
	mMCD	50·3% (42-59; 74/147)	45·5% (38-53; 81/178)	48·9% (40-57; 68/139)
	FCD I	57·7% (51-64; 124/215)	53·2% (47-60; 132/248)	54·5% (46-62; 85/156)
MCD-other		53·4% (48-58; 220/412)	52·3% (47-57; 212/405)	51·2% (45-57; 148/289)
	hypothalamic hamartoma	43·2% (34-52; 54/125)	43% (34-53; 46/107)	49·3% (38-61; 36/73)
	tuber	52·1% (43-61; 62/119)	50% (41-59; 58/116)	45·4% (35-56; 44/97)
	MCD-other	61·9% (54-69; 104/168)	59·3% (52-66; 108/182)	57·1% (48-66; 68/119)
FCD-NOS		71·3% (67-76; 303/425)	69·7% (65-74; 288/413)	59·5% (52-66; 122/205)
Non LEAT		72·3% (67-77; 251/347)	68·4% (63-73; 212/310)	67·6% (61-74; 152/225)
	oligodendroglioma	67·2% (58-75; 80/119)	66·4% (56-75; 71/107)	67·9% (56-78; 55/81)
	tumour-other	75·0% (69-80; 171/228)	69·5% (63-76; 141/203)	67·4% (59-75; 97/144)
Glial scar		62·1% (56-68; 149/240)	59·4% (53-65; 155/261)	56·1% (48-64; 96/171)
Encephalitis		67·2% (58-75; 90/134)	59·7% (50-68; 74/124)	54·5% (44-65; 48/88)
	encephalitis-other	51·8% (38-65; 29/56)	42·3% (29-57; 22/52)	50% (34-66; 18/36)
	Rasmussen	78·2% (67-86; 61/78)	72·2% (60-82; 52/72)	57·7% (43-71; 30/52)
Total		**71·8% (71-73; 5921/8247)**	**67·5% (66-69; 5530/8191)**	**66·2% (65-67; 3693/5577)**

Legend to Table 2: The proportions (95% confidence interval; absolute numbers) of the main categories of histopathological diagnosis correspond to Figure 1. DNET = Dysembryoplastic neuroepithelial tumour. FCD = focal cortical dysplasia. MCD = malformation of cortical development. mMCD = mild MCD. NOS = not otherwise specified. LEAT = low-grade epilepsy associated neuro-epithelial tumour. LGNET = Low-grade neuroepithelial tumour.

Figure 1 | Proportion of patients who (A) were free from disabling seizures and (B) free from both disabling seizures and AEDs.



Legend to Figure 1: Proportions of patients who (A) were free from disabling seizures (Engel 1/ILAE 1-2) at 1 (n=5,921/8,247), 2 (n=5,529/8,191) and 5 (n=3,693/5,577) years after surgery, and (B) both Engel 1 and AED free at 1 (n=323/5,861), 2 (n=881/5,461) and 5 (n=1,250/3,753) years after surgery. The exact proportions corresponding to this figure are indicated in (A) Table 2 and (B) Table 3. For the same information on cases with information available on all three follow-up time-points, see the complete case Appendix pages 5 and 6. FCD = focal cortical dysplasia. HS = hippocampal sclerosis. MCD = malformation of cortical development. mMCD = mild MCD. NOS = not otherwise specified. LEAT = low-grade epilepsy associated neuro-epithelial tumour. Error bars indicate 95% confidence intervals.

Figure 1 plots the proportion of patients free from disabling seizures per diagnostic category, from one to five years postoperatively. As a sensitivity analysis, this figure was recreated using the subset of patients for whom seizure outcome was known at all three time points, yielding similar rates and their change over time (Appendix page 5). The decline in favourable outcome from one to five

postoperative years differed between the categories, with a decrease of 9% (7/82) for those with encephalitis, and 2% for non-LEAT (4/220, Appendix page 7).

Factors independently associated with Engel 1 outcome were histopathology, location of surgery, duration of epilepsy and age at surgery (Appendix page 9). Multivariable regression analysis including interaction effects between duration, age at surgery and the eleven main histopathology categories (Appendix page 9) revealed that, compared to LEAT, the chance of reaching Engel class 1 at two years was lower for the diagnostic categories no lesion (odds ratio (OR) 0·36, 95% uncertainty interval (UI) 0·30-0·46), FCD I/mMCD (0·38, 0·28-0·49), encephalitis (0·43, 0·22-0·73), MCD-other (0·44, 0·29-0·63), scar (0·53, 0·39-0·70), and hippocampal sclerosis (0·79, 0·65-0·89) (Appendix page 9). Seizure-outcome in LEAT patients was not different from that in patients with non-LEAT (0·75, 0·54-1·02), vascular malformation (0·78, 0·60-1·06), FCD II (0·80, 0·61-1·09), and FCD-NOS (0·83, 0·59-1·09) (Appendix page 9).

The proportion of patients both Engel 1 and AED-free is displayed in Figure 1B, Table 3, and Appendix page 10. Engel 1 and drug-freedom rates increased over time, varying between 0% to 14% at one year and 14% to 51% at five years, depending on histopathology. After adjusting for potential confounders, the relation between histopathology and Engel 1 and drug-freedom at five years was similar to that between histopathology and freedom from disabling seizures (Appendix page 11). People with LEAT were more often drug-free at five years after surgery, compared with patients with scar (OR 0·22, 95% UI 0·10-0·34), encephalitis (0·27, 0·17-0·75), FCD I/mMCD (0·28, 0·22-0·46), no lesion (0·28, 0·24-0·42), non-LEAT (0·45, 0·29-0·66), MCD-other (0·46, 0·26-0·75), FCD-NOS (0·62, 0·54-0·97), and hippocampal sclerosis (0·64, 0·65-0·89) (Appendix page 11). There was no difference in Engel 1 and AED-freedom between patients with LEAT and vascular malformations (0·71, 0·77-1·36), and FCD II (0·79, 0·75-1·27) (Appendix page 11). Independent determinants of Engel 1 and drug-freedom at five years were histopathology, younger age, temporal surgery, and shorter epilepsy duration.

Table 3 | Proportion of patients who were both free from disabling seizures (Engel 1) and had completely discontinued antiepileptic drugs at 1, 2 and 5 years after surgery by histopathological diagnosis.

Histopathological diagnosis	1 year (n = 5861)	2 years (n = 5461)	5 years (n = 3753)

Hippocampal sclerosis		5·5% (5-7; 123/2228)	13·2% (12-15; 257/1940)	32·8% (30-35; 423/1290)
LEAT		5·2% (4-7; 48/924)	22·9% (20-26; 205/896)	47·1% (43-51; 288/612)
	LGNET	4·9% (1-18; 2/41)	17·7% (10-30; 11/62)	42·3% (29-57; 22/52)
	DNET	6·9% (5-10; 27/392)	21·4% (17-26; 74/346)	44·7% (38-51; 109/244)
	ganglioglioma	3·9% (2-6; 18/458)	25·2% (21-29; 115/457)	51·0% (45-57; 149/292)
	LEAT-other	3·0% (0-18; 1/33)	16·1% (6-34; 5/31)	33·3% (16-55; 8/24)
FCD II		5·8% (4-8; 29/504)	15·8% (13-19; 86/545)	34·9% (30-40; 147/421)
No lesion		3·4% (2-5; 20/593)	10·4% (8-13; 61/584)	20·2% (16-25; 77/381)
	gliosis	3·1% (2-5; 14/454)	10·6% (8-14; 50/470)	22·1% (18-27; 65/294)
	normal tissue	4·3% (2-10; 6/139)	9·6% (5-17; 11/114)	13·8% (8-23; 12/87)
Vascular malformation		6·7% (4-10; 21/315)	24·8% (20-30; 74/298)	36·6% (30-44; 70/191)
	vascular-other	11·5% (6-21; 10/87)	27·4% (18-38; 23/84)	36·5% (25-50; 23/63)
	cavernoma	4·8% (3-9; 11/228)	23·8% (18-30; 51/214)	36·7% (29-46; 47/128)
FCD I/mMCD		1·6% (0-4; 4/258)	7·1% (4-11; 19/268)	19·5% (15-25; 43/221)
	mMCD	0% (0-5; 0/102)	9·3% (5-16; 11/118)	25·3% (17-35; 25/99)
	FCD I	2·6% (1-7; 4/156)	5·3% (3-11; 8/150)	14·8% (9-23; 18/122)
MCD-other		9·3% (6-14; 23/247)	20·3% (15-26; 44/217)	30·1% (23-38; 52/173)
	hypothalamic hamartoma	16·4% (9-28; 11/67)	19·6% (10-34; 9/46)	21·2% (10-39; 7/33)
	tuber	3·1% (1-12; 2/64)	11·3% (5-22; 7/62)	21·6% (12-36; 11/51)
	MCD-other	8·6% (4-16; 10/116)	25·7% (18-35; 28/109)	38·2% (28-49; 34/89)
FCD-NOS		6·4% (4-10; 20/314)	19·7% (15-25; 59/300)	37% (29-45; 57/154)
Non-LEAT		6·5% (4-11; 16/246)	19·5% (14-26; 40/205)	32·9% (26-41; 50/152)
	oligoastrocytoma	6·8% (3-15; 6/88)	14·7% (8-25; 11/75)	31·2% (21-44; 20/64)
	tumour-other	6·3% (3-12; 10/158)	22·3% (16-31; 29/130)	34·1% (25-45; 30/88)
Glial scar		5·6% (3-11; 8/144)	12·3% (7-20; 16/130)	24·3% (17-34; 25/103)
Encephalitis		12·5% (7-22; 11/88)	25·6% (17-37; 20/78)	32·7% (21-47; 18/55)
	encephalitis-other	10·3% (3-28; 3/29)	21·4% (9-41; 6/28)	15·8% (4-40; 3/19)
	Rasmussen	13·6% (6-26; 8/59)	28% (17-43; 14/50)	41·7% (26-59; 15/36)
Total		**5·5% (5-6; 323/5861)**	**16·1% (15-17; 881/5461)**	**33·3% (32-35; 1250/3753)**

Legend to Table 3: The proportions (95% confidence interval; absolute numbers) of the main categories correspond to Figure 1B. DNET = Dysembryoplastic neuroepithelial tumour. FCD = focal cortical dysplasia. MCD = malformation of cortical development. mMCD = mild MCD. NOS = not

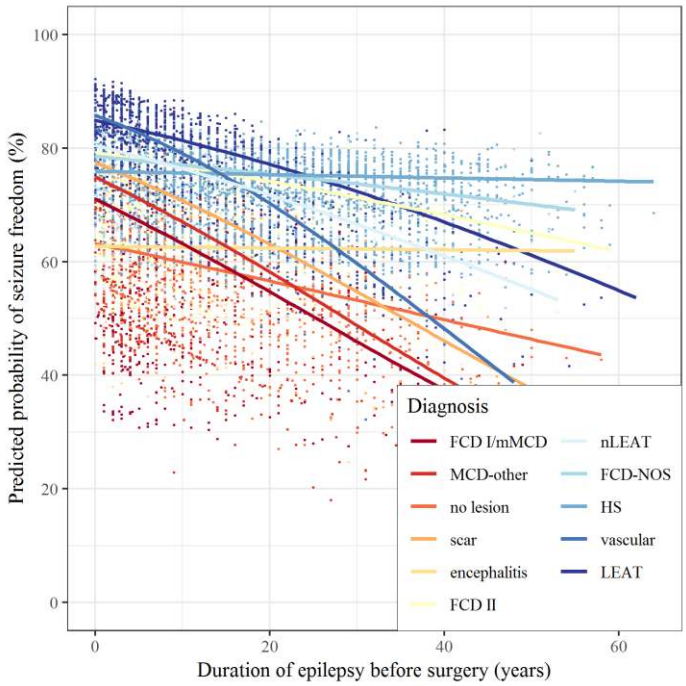
otherwise specified. LEAT = low-grade epilepsy associated neuro-epithelial tumour. LGNET = Low-grade neuroepithelial tumour.

The proportion of patients free from disabling seizures varied between centres, with an interquartile range of 62-74% seizure-free patients at five years (Appendix page 12). For Engel 1 and drug-freedom at five years the variation between centres was much larger, with an interquartile range of 18-37% (Supplementary Figure 5). For the categories of pathology, variation in Engel 1 outcome at two years was plotted, showing even larger variation between centres (Appendix page 13), which decreased when selecting only centres with at least 10 included cases for the specific diagnosis decreases this variation (Appendix page 14).
This natural variation between centres was effectively modelled with random intercepts in the multivariable models.

Differential effect of duration of epilepsy

The effect of duration on seizure-outcome varied across different diagnoses. Figure 2 visualises the difference in the effect of duration on outcome between the diagnoses. As an example, Engel 1 rates of patients with LEAT in the temporal lobe were 84% at two years when surgery is performed within a year after epilepsy onset, but decreased to 77% after a duration of 20 years. A similar pattern is seen for the other diagnoses, except hippocampal sclerosis.

Figure 2 | Predicted probabilities of freedom from disabling seizures (Engel 1/ILAE 1-2) at two years for the different diagnoses, plotted against duration of epilepsy.



Legend to Figure 2: Individual dots indicate predicted probability of included patients, based on the model presented in Appendix page 9. Lines are the average predicted probability for each histopathological diagnosis (with age at surgery 27, year of surgery = 2007, and location = temporal). FCD = focal cortical dysplasia. HS = hippocampal sclerosis. MCD = malformation of cortical development. mMCD = mild MCD. NOS = not otherwise specified. LEAT = low-grade epilepsy associated neuro-epithelial tumour.

Comparing adults and children

Overall, children had equal Engel class 1 outcomes at five years compared to adults (67% and 66%, respectively. There was some variation between histopathology classes, however (Appendix page 15). Age at surgery as continuous variable does not seem to be related to seizure outcome at two years (OR 0·99, 95% UI 0·98-1·00) for LEAT (Appendix page 9). The only histopathology class for which the uncertainty interval for the interaction effect with age does not contain 1 is FCD I/mMCD, meaning that the effect of age on outcome is significantly different for this class. In the case of FCD I the OR would approximately be 0·99*1·03 = 1·02, slightly favouring older age.

Appendix page 15 displays the comparison between children and adults regarding Engel 1 outcome and drug-freedom, with even larger differences between the two groups. For all categories, children were more often seizure- and drug-free (45%) as compared to adults (28%), depending on the diagnosis.

Complete seizure-freedom rates (Engel 1a)

Complete seizure freedom rates (Engel class 1a: free from seizures including aura's since surgery) were only available in a subset of patients. On average these were 11% lower than the freedom from disabling seizures (Engel class 1) (Appendix page 16).

Discussion

In this large multi-centre cohort study of 9,147 patients who underwent epilepsy surgery across eighteen European countries, histopathological diagnosis was an important and independent determinant of outcome. The average proportion of patients Engel class 1 was 68% at two years post-surgery, varying from 78% in patients with low-grade brain tumours to 50% in those classified as FCD I or mMCD. From one to five years after surgery, these rates dropped in the range of 2% to 9%, depending on the underlying brain lesion and least so in patients with vascular lesions and tumours. Independent determinants of freedom from disabling seizures and of Engel 1 and drug-freedom were histopathology, younger age at surgery, temporal lobe location of surgery, and a shorter disease duration before surgery.

Children had an equal prognosis regarding seizure-outcome compared to adults, but more children discontinued medication. Our study revealed that children undergo more often a resection outside the temporal lobe, less often have a diagnosis of hippocampal sclerosis, and more often suffer from pathologies that are known to have worse outcomes, such as encephalomalacia (histopathologically classified as glial scar). Despite this relatively unfavourable prognostic profile, surgery in childhood was overall associated with equal surgical outcomes, independent of an inherently shorter duration of epilepsy in this group of patients.

The one-year seizure-outcomes in this study – and their correlation with histopathological diagnoses – resembled those from a previous EEBB report[5]. The exact proportions of seizure-freedom, however, are higher in the current study, which can be explained by the different recruitment scheme between both studies including different time periods and a less stringent seizure-outcome definition (Engel 1, as compared to Engel 1A in the previous study).

Previous large studies have analysed the relation between histopathology and surgery outcomes[10–12,15,20,21]. Reported seizure-freedom was between 49% and 73%, at various time intervals after surgery, and the only aetiology that was uniformly characterised in all studies was hippocampal sclerosis. The recognition of other aetiologies varied considerably across studies, rendering comparison of different brain lesions problematic. Our large collection of data bridges this gap and provides a comprehensive overview of histopathology entities and seizure outcome at 1, 2 and 5 years after surgery. Several studies have suggested that shorter disease duration is a predictive measure for better outcome[10,22–25] , substantiated by a recent aggregate meta-analysis[26]. We obtained identical results (Figure 2). The absence of an effect of duration for the hippocampal sclerosis patients is difficult to explain, although other studies have reported similar results, with duration having an effect on outcome except in hippocampal sclerosis[10,22,27]; only one study showed a possible effect for hippocampal sclerosis patients specifically[23]. The association between shorter duration and better outcomes could either be causal, e.g. there is a pathophysiological epileptogenic process in which longer epilepsy duration before surgery creates circumstances decreasing the chance of success. An alternative hypothesis is that the cases that are considered by the treating physician to have a high chance of surgical success are operated earlier than those where there is more doubt about the merit of surgery. Within patients with hippocampal sclerosis there may not be such a strong contrast between more or less complex cases.

In contrast to the other known predictors of surgical outcome – duration of epilepsy is the only factor that can be influenced by decisions made after the diagnosis of drug-resistant epilepsy. Many studies have shown a delay in referral of patients with focal epilepsy to a specialised epilepsy surgery centre[28–31], with an average time between onset and surgery of twenty years in adults[5]. Another factor might be the patients' perspective on epilepsy surgery. A recent study among German epileptologists and patients[32] found that only one in three patients followed the epileptologists' recommendation to enter presurgical evaluation. This is often caused by fear for possible postoperative handicaps or cognitive deficits. It is also related to the lack of complete success of surgery in >25% of cases. Counselling on the expected benefits and low risks of surgery to patients, and improving referral practices from secondary to tertiary care may shorten the duration until surgery and improve outcomes.

Although 51-76% of patients within the eleven main categories were free from disabling seizures (Engel class 1), only 20-47% of them were both seizure and drug-free at five years. This contrast was more pronounced in adults, where only 10-40% was Engel 1 and drug-free at five years, compared to 26-57% of children. The fact that children withdraw from medication more often and earlier than

adults was already observed in a Swedish national study[24]. A major contributing factor for the difference between adults and children are the consequences of AED withdrawal and the risk of seizure recurrence. For adults these consequences may have a much larger impact, for example by losing the ability to drive[33], but also factors like occupation and stigma could play a role. In children surgery might be considered a means to avoid life-long treatment with AEDs. Hence, these differences may not reflect a difference in seizure control without AEDs, but rather the different attitudes in AED policy decision making between adult patients and children and their care-givers.

Strengths and limitations

This is the largest study on histology findings in epilepsy surgery with seizure and drug outcome data available at 1, 2 and 5 years after surgery. Including more than 9,000 patients allowed for precise analyses of the effects on seizure outcome for all aetiologies separately, and of the independent effect of duration of epilepsy within subgroups. Epilepsy surgery outcomes are usually presented for cohorts of only several hundreds of patients, limiting the possibilities of subgroup analysis or correcting for multiple confounding factors. Many studies dichotomise, therefore, between temporal and extratemporal lobe surgeries, or assemble smaller aetiologies together into “others”.

Our histopathology-based approach allowed a reliable phenotyping of patients with low chance of misclassification. However, sampling errors of surgical specimens cannot be excluded as they may occur at the margin of focal resections, in the case of "dual pathology" with adequate sampling of the hippocampus but not of cortical tissue, and when sampling one small part of a large and complex cortical malformation.

In addition, in a small proportion of the no-lesion group the primary pathological tissue may not have been sent for review or left in place after being disconnected, as often is the case in hemispheric surgeries (i.e. sampling error). However, the majority of patients in the no-lesion group had TLE without microscopic evidence of hippocampal sclerosis.

Drawing causal inferences from observational data is an inherent difficulty challenging our conclusions on the effect of duration of epilepsy. Interestingly, the beneficial effect of short disease duration remained after correcting for the confounders age at surgery, histopathology, and surgery lobe. Other probable confounders were not available for analysis, however, such as preoperative MRI data, EEG characteristics, completeness of resection and resection volume, and medical and seizure history[6–9], which may influence the true effect. Complexity of the epilepsy syndrome may have confounded the relation between duration of epilepsy and outcome. The presurgical evaluation trajectory – and possibly also the time interval before referral to a surgical centre – may have been

longer in patients with less straight-forward focal structural epilepsies, in whom the need for more presurgical diagnostic investigations inherently reflects a lower chance of surgical success[6,7].

Due to the retrospective design of the data collection, with a predefined fixed set of requested variables, not all clinical parameters were available and data entries have not been standardised. Quality control of the database was continuously monitored in 4.9% of included patients and in a randomized cohort of 1% of patients, which yielded a deviation of 0.4% of our datasets. The outcome data were not complete for all three time-points in all patients. The sensitivity analyses using only those patients with all three outcomes available, however, showed no discrepancies when compared to the main results presented in this study. By imputing missing data for the logistic regression this problem is largely overcome[19]. We should acknowledge that not including patients of whom no histopathological data were available, such as some undergoing disconnection surgery, could have introduced a bias when assessing the relation between aetiology and outcome.

Finally, we used an imperfect measure for seizure outcome. Engel class 1 contains four subdomains, of which only Engel class 1a entails complete seizure freedom ever since surgery (similar to ILAE class 1). Formally, we have therefore not reported seizure-freedom after surgery, which has two consequences for the interpretation of results: (1) in a small proportion of patients with good outcome, we don't know whether surgery with curative intent had been fully successful, and (2) discontinuation of medication is not possible for everyone with an Engel class 1 score, explaining part of the discrepancy between freedom from disabling seizures and drug-freedom.

In conclusion, this patient cohort from the European Epilepsy Brain Bank allowed for comparison of surgery outcome across all major disease aetiologies. The percentage of patients free from disabling seizures dropped from 72% at one year postoperatively to 66% at five years, with important differences between histopathological diagnoses. Apart from histopathology, important factors associated with good outcome after surgery are a short duration of epilepsy, young age at surgery, and when the temporal lobe was targeted for surgery.

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Declarations of conflict of interest

HJL[1], KPJB[1], WGMS[1], WO[1], KG[1], AM[1], EA[1], FJ[1], FL[1], PvR[1]; IB[2], RC[2], KR[2], BSK[2]; TC[3], TP[3], TK[3], SF[3], AG[3]; JS[4], AB[4], DD[4], CEE[4]; JSD[5], JDT[5], AM[5], AME[5], MT[5]; FC[6], PV[6], EL[6], BT[6], BD[6]; GD[7], CB[7], MF[7], FSF[7], MC[7]; KM[8], AE[8], BR[8]; ASB[9], CS[9], VSAA[9], MJS[9], JB[9]; EGD[10], MT[10], CE[10], TJS[10]; CÖ[11], BO[11], SA[11], KD[11], MU[11]; TP[12], HH[12], TH[12], MK[12], MS[12]; GDG[13], SC[13], PPQ[13], FG[13], VE[13]; JI[14], NS[14], MG[14], HC[14]; IB[15], AV[15], AC[15], NM[15], MH[15]; PM[16], JZ[16], MT[16], AK[16];AI[17], TR[17], AS[17], LJ[17]; SM[18], MS[18], JAL[18], KE[18], KLS[18]; SN[19], EH[19], HL[19], KE[19]; JK[20], KK[20]; LV[21], WVP[21], JVL[21], TT[21], EC[21], RS[21]; AM[22], PV[22], AK[22], AV[22], LS[22]; MF[23], TC[23], GG[23], JAH[23], SS[23], TS[23]; JP[24], IA[24]; GP[25], SW[25], GZ[25], HS[25], MA[25]; RG[26], RS[26], FD[26], LR[26], FV[26]; AH[27], CN[27], BC[27]; PK[28], AB[28], BB[28], MK[28]; OS[29], JB[29], JCB[29], GH[29], AC[29], VKM[29], RPWR[29]; JA[30], JR[30], ARC[30], SCC[30]; AA[31], PKK[31], AM[31], KOC[31], CM[31], ZGS[31], EP[31], JT[31]; RG[32], CB[32], AMB[32], FG[32]; AJ[33], VS[33], AD[33], GM[33], ZPG[33]; NS[34], CEM[34], ADB[34], GCP[34], LDP[34]; SR[35], VB[35], AR[35], NV[35], DS[35]; JR[36], OR[36], FS[36]; AGN[37], AAS[37], IGM[37], CA[37], RT[37] declare no conflict of interest.

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