Long-term outcomes of epilepsy surgery

Prospective studies regarding seizures, employment and quality of life

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Electrical brain by Maria Nilsson

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”What’s the most difficult part of coping with epilepsy?”

“The memory loss, the fatigue,
the school I miss because of fatigue
and seizures, the fear that the next one
may kill me, knowing I’m killing my body
with my meds but needing them to survive.”

“It hurts physically, emotionally, economically and socially.”

From The Epilepsy Network Facebook community, November 2016

Abstract

Epilepsy surgery is a treatment option for selected patients with drug-resistant epilepsy. Patients need individual pre-surgical counselling on chances of seizure freedom and other outcomes in a long-term perspective. The aim of this thesis was to investigate long-term outcomes as to seizures, antiepileptic drugs (AEDs), employment and health-related quality of life (HRQOL) and to investigate prognostic factors for seizure and employment outcomes.

All three studies were prospective, longitudinal and population-based. Study I and II were based on outcome data from the Swedish National Epilepsy Surgery Register. Study III was a controlled prospective, cross-sectional, national long-term follow-up study 14 years after epilepsy surgery evaluation where HRQOL was investigated using the 36-item Short Form Health Survey.

In Study I, 62% of adults and 50% of children were seizure-free at long-term (5 or 10 years after surgery). Predictors for seizure freedom were MRI abnormalities, lower seizure frequency at baseline and shorter duration of epilepsy. At 10 years, 86% of seizure-free children and 43% of seizure-free adults had discontinued AED medication.

In Study II, employment rates were mainly unchanged at group level 5, 10 and 15 years after surgery. Predictors for postoperative employment were pre-operative employment, seizure freedom and younger age. Only 57% and 47% of those who were employed full-time before surgery and became seizure-free were still in full-time employment 10 and 15 years after surgery. Out of the seizure-free patients who had been on benefits or sick leave before surgery, 30% were employed full-time at long-term follow-up. Compared to the general population fewer patients worked up to the age of 65.

In Study III, HRQOL scores were compared to non-operated controls and to a matched norm population. At long-term, operated patients reached norm values on all domains except Social Functioning and Mental Health, whereas controls scored lower than norm on five of eight domains. Changes in HRQOL were small from two-year to long-term follow-up. Change in seizure status for the operated patients did not influence HRQOL results.

In conclusion, long-term seizure freedom was achieved by 50-60%. Post-operative discontinuation of AEDs was common especially in seizure-free children. Many adults could continue or go back to work, and HRQOL was better at group level for operated patients than for controls. Younger age at surgery and shorter epilepsy duration were predictive of better results, indicating the importance of earlier referrals for pre-surgical evaluation.

Sammanfattning på svenska

Epilepsi är den vanligaste kroniska neurologiska sjukdomen och det finns ca 60,000 personer med epilepsi i Sverige. Epilepsi kan vara generaliserad eller fokal. Vid fokal epilepsi finns anfallsursprunget i ett avgränsat område i hjärnan, och för en del av dem som inte når anfallsfrihet med mediciner finns möjligheten till behandling med epilepsikirurgi. Under den pre-operativa utredningen försöker man att lokalisera anfallsursprunget så exakt som möjligt, och avgöra närheten till känsliga områden. Det är viktigt att kunna ge bra information till patienterna om möjliga risker och vinster, innan man kommer till beslut om att operera eller ej.

Avhandlingens syfte var att studera resultaten av epilepsikirurgi på lång sikt (minst fem år) avseende anfall, medicinering, arbete och hälsorelaterad livskvalitet.

De första två studierna i avhandlingen baseras på Svenska Epilepsikirurgi-registret. Dit rapporteras data i samband med utredningen inför operationen, efter operationen och sedan efter två år. Därefter sker uppföljningar vart femte år. I den första studien jämfördes anfallssituation och epilepsimedicinering fem och tio år efter epilepsikirurgi med en kontrollgrupp som hade utretts för kirurgi men inte opererats. Vid uppföljningen var 62 % av de opererade vuxna och 50 % av barnen anfallsfria, jämfört med 14 % av de icke-opererade vuxna och 38 % av barnen. Faktorer som innebar högre sannolikhet för anfallsfrihet var avvikande fynd på magnetkameraundersökning, lägre anfallsfrekvens före operationen och kortare sjukdomstid. Efter tio år hade 43 % av de anfallsfria vuxna och 86 % av de anfallsfria barnen helt slutat med epilepsimediciner. Bland de icke-opererade var ingen medicinfri.

Den andra studien beskriver i hur stor utsträckning vuxna som har opererats för epilepsi arbetar efter 5, 10 och 15 år. I hela gruppen av opererade patienter sågs ingen stor förändring av antalet heltidsarbetande, men när man delade upp patienterna i grupper utifrån arbetssituation före operationen sågs flera skillnader. De med heltidsarbete före operation och som sedan blev anfallsfria hade bäst resultat, men andelen som fortsatte att

arbeta heltid sjönk successivt. Ca 30 % av dem som hade bidragsförsörjning före operationen (dvs. var arbetslösa, sjukskrivna eller hade sjukpension/sjukersättning) och som blev anfallsfria, arbetade heltid efter fem och tio år. Jämförelser gjordes med befolkningen i allmänhet, uppdelat i åldersgrupper. De visade att opererade personer som blivit anfallsfria arbetade heltid i något mindre grad än befolkningen i allmänhet. Mot slutet av arbetslivet sjönk andelen patienter med heltidsarbete. Faktorer som innebar högre sannolikhet för arbete efter operation var arbete före operationen, lägre ålder vid operationen samt uppnådd anfallsfrihet.

I den tredje studien ingick patienter som utreddes eller opererades i Sverige 1995-1998. Dessa personer svarade på en enkät om hälsorelaterad livskvalitet (SF-36) under utredningen, efter två år och efter i genomsnitt 14 år. Vid långtidsuppföljningen hade de som opererats samma resultat som en ålders- och könsmatchad svensk referensgrupp, utom för områdena social funktion och mental hälsa. Icke-opererade patienter hade lägre nivåer än referensgruppen inom fem av åtta områden. På individnivå undersöktes hur stor andel som förbättrades och försämrades mer än 'minsta betydelsefulla förändring'. Hälften av de opererade upplevde förbättring av fysisk eller mental hälsa, jämfört med ca en tredjedel av de icke-opererade. Försämring av fysisk eller mental hälsa angavs av en femtedel av de opererade och en tredjedel av icke-opererade.

Sammanfattningsvis var kortare sjukdomstid och lägre ålder faktorer som var associerade med anfallsfrihet och att ha arbete. Livskvaliteten skattades högre av opererade än av icke-opererade personer med epilepsi. Detta illustrerar betydelsen av att tidigt identifiera patienter som har nytta av epilepsikirurgi. I rådgivningen inför kirurgi är det viktigt att kunna ge individualiserad information om förväntade vinster och risker även på lång sikt.

List of papers

This thesis is based on the following studies, referred to in the text by their Roman numerals:

I. Edelvik A, Rydenhag B, Olsson I, Flink R, Kumlien E, Källén K, Malmgren K. Long-term outcomes of epilepsy surgery in Sweden: a national prospective and longitudinal study. *Neurology, 2013. 81(14): p.1244-1251.*

II. Edelvik A, Flink R, Malmgren K. Prospective and longitudinal long-term employment outcomes after resective epilepsy surgery. *Neurology, 2015. 85(17): p. 1482-1490.*

III. Edelvik A, Taft C, Malmgren K. Health-related quality-of-life and emotional wellbeing after epilepsy surgery - a prospective, controlled, long-term follow-up. *Manuscript.*

Contents

Abbreviations

AED	Antiepileptic drug
B	Patients on benefits (unemployed, sick leave, disability pension)
CT	Computed tomography
EEG	Electroencephalography
FLR	Frontal lobe resection
FW	Full-time work
HAD	Hospital Anxiety and Depression scale
HAD-A	Hospital Anxiety and Depression scale – anxiety subscale
HAD-D	Hospital Anxiety and Depression scale – depression subscale
HRQOL	Health-related quality of life
ILAE	International League Against Epilepsy
MCID	Minimum clinically important difference
MCS	Mental Component Summary
MRI	Magnetic resonance imaging
NO	Non-operated patients
Op	Operated patients
OpF	Operated seizure-free patients
OpS	Operated not seizure-free patients
OR	Odds ratio
PCS	Physical Component Summary
PW	Part-time work
R	Retired (old-age pension)
RCT	Randomized controlled trial
S	Students
SF-36	The 36-item Short Form Health Survey
SGTCS	Secondary generalized tonic-clonic seizures
SNESUR	The Swedish National Epilepsy Surgery Register
SRM	Standardized Response Mean
TLR	Temporal lobe resection
QOLIE-31	The Quality of Life in Epilepsy Inventory, 31 items
QOLIE-89	The Quality of Life in Epilepsy Inventory, 89 items

1 Introduction

Epilepsy is one of the most common chronic neurological diseases and affects more than 50 million people worldwide, according to the World Health Organization.[1] In Sweden there are about 60,000 persons with epilepsy, 10,000 of whom are children.[2, 3]

Epilepsy is characterized by recurrent, spontaneous, synchronous, uncontrolled electrical discharges of the brain nerve cells, resulting in repeated seizures. The seizure symptoms depend on which parts of the brain that are involved. Some seizures are confined to a small volume of the brain, and may lead to symptoms only noticed by the patient him/herself, while others are more widespread and may lead to impairment of consciousness and sometimes generalized convulsions. Seizures can vary widely in frequency, with some patients experiencing only a few seizures in their whole life time, while others can have many seizures every day. The consequences of having epilepsy are multiple and vary in severity, but all patients share the uncertainty of not knowing when the next seizure will occur. The impact on daily life includes e.g. driving restrictions, cognitive impairments associated with epilepsy or medication, psychiatric and other comorbidities and risk of injuries. Fear, ignorance, social stigma and discrimination are long-standing societal problems associated with epilepsy, and continue to be obstacles that contribute to reduced quality of life for many persons with epilepsy.

It has long been understood that epilepsy is a disorder affecting the brain. Hippocrates is believed to have written one of the first recorded observations of epilepsy in humans around 400 BC stating that it is a physical disease originating in the brain.[4] This understanding fell into oblivion and for many centuries epilepsy has been surrounded by prejudice and myths. One of the major contributors to the more modern understanding of epilepsy was the English neurologist John Hughlings Jackson, who in 1873 stated that “epilepsy is the name for occasional, sudden, excessive, rapid, and local discharges of grey matter”. Treatments for epilepsy have been diverse and often bizarre through history, and it was

not until the second half of the 19th century that the first effective pharmacological treatment emerged. Up to the 1970s only a handful of antiepileptic drugs (AEDs) were available, but since then a large number of new drugs have been developed. Despite the increasing number of AEDs, around 30% of persons with epilepsy continue to have seizures.[5] For some of these patients epilepsy surgery is the treatment of choice.

1.1 Classifications of seizures and epilepsies

The classification of epilepsy encompasses two areas; the classification of seizure types and the classification of epilepsy syndromes and aetiological factors. Both concepts have been extensively discussed and the classification systems have undergone several adjustments and are currently under revision by the professional medical organisation, the International League Against Epilepsy (ILAE).[6-8]

Seizure classification

In the current proposal of operational definitions of seizures, there is a general division between seizures that originate in a defined or more localized part of the brain (focal seizures, previously denoted "partial seizures"), or seizures that originate within widely distributed networks comprising large parts of the brain (generalized seizures), or seizures of unknown onset.[9] The symptoms and clinical manifestations of seizures (denoted seizure semiology) and electroencephalography (EEG) findings comprise the basis for classification into focal or generalized onset. The focal symptoms have a localizing value and reflect the functional properties of the brain areas involved. Focal seizures can occur without affecting the patient's consciousness or awareness (previously denoted "simple partial seizures") or with impairment of awareness (previously termed "complex partial seizures"). The new terminology proposals are "focal aware" and "focal seizure with impaired awareness", respectively. Focal seizures can evolve and engage large parts of or the entire brain, leading to generalized tonic-clonic convulsions. These were previously denoted "partial (or focal) with secondary generalization", the new proposed term being "focal to bilateral tonic-clonic".

Generalized seizures are seizures where the initial clinical and EEG changes point to a widespread start of seizure activity in large areas of both hemispheres, without indications of anatomical localization. The underlying disturbance is thought to arise from a general imbalance between excitatory and inhibitory systems, presumably of genetic origin. The main generalized seizure types include generalized seizures with motor symptoms (the most common types are tonic-clonic and myoclonic seizures) and generalized absence seizures (non-convulsive).

Classification of epilepsies and syndromes

As well as a new classification system for seizures, there is ongoing work with development of a 'road map' for the classification of epilepsy syndromes, with newly developed terms and concepts.[10] The details of this extensive work will not be covered here and the proposal is still open to suggestions and amendments. In general, several axes are proposed as a framework for syndrome and aetiology classification, where seizure types, aetiology and comorbidities are part of the scheme. The main groups of underlying aetiologies are genetic, structural, metabolic, immune, infectious and unknown. Some syndromes may have more than one aetiology, which makes the classification process even more complicated.

1.2 Epidemiology

The prevalence of epilepsy in Europe has been shown to vary between 6 and 7 per 1000 adults, and somewhat lower in children and adolescents, 4.5-5 per 1000 persons. The incidence is higher in infancy and early childhood as well as in the elderly, and an average of about 50 per 100,000 person-years has been estimated in northern Europe.[11,12] The main reasons for the age-related incidence peaks are congenital disorders in children and stroke in the elderly. Brain tumours, trauma and neurodegenerative diseases (in particular Alzheimer's disease) are other common reasons for epilepsy in adults. Focal epilepsy is more common than generalized and accounts for about two thirds of the cases, but the proportions vary widely across studies.[12] Intellectual disability is more common in individuals with epilepsy,[2] as are autism spectrum disorders.[13] There is a bilateral

relationship between epilepsy and mood disorders. Patients with epilepsy have a higher risk of developing psychiatric disorders and persons with primary psychiatric disorders are at greater risk of developing epilepsy.[14]

1.3 Antiepileptic drug treatment

Antiepileptic drugs (AEDs) are the base for treatment of epilepsy. Their mechanisms of action are not always completely known, but can involve either an increase of the inhibitory activity, or a decrease of the excitatory activity involved in seizure generation. Medical treatment is symptomatic (i.e. suppresses seizures) but does not cure epilepsy per se. Around two thirds of patients achieve seizure freedom with AEDs, and the newer drugs have not proven to be more efficient.[5] If seizure freedom is not reached drugs are used in combination (polytherapy). Many patients experience dose related side effects that may limit the possibility to use the AED to its full potential and which may lower the patients' quality of life.[15] Drug resistant epilepsy is defined as failure of adequate trials of two tolerated and appropriately chosen AEDs (in monotherapy or in combination) to achieve seizure freedom.[16] In 2003 the American Academy of Neurology published a practice parameter stating that patients with 'disabling complex partial seizures' should be referred to an epilepsy surgery centre when first-line treatments had failed.[17] For children, a consensus recommendation was published some years later emphasizing that the negative effect of uncontrolled seizures on cognitive and behavioural development should prompt early assessment by paediatric epilepsy centres.[18]

1.4 The history of epilepsy surgery

One of the early landmarks in the history of epilepsy surgery was when the British neurosurgeon Victor Horsley successfully performed brain surgery on a young man with posttraumatic epilepsy in 1886.[19] EEG was introduced by Hans Berger in 1929 and revolutionized the electrophysiological understanding of epilepsy and helped identify the temporal lobe as an important target for epilepsy surgery. Beginning their work in the 1930s at

the Montreal Neurological Institute in Canada, neurosurgeon Wilder Penfield and neurologist Herbert Jasper were of monumental importance in the development of epilepsy surgery and in the per-operative study of cortical functions. The modern development of time-locked video-EEG (when EEG and videos of seizures are recorded synchronously) and advanced neuroradiology, particularly magnetic resonance imaging (MRI), have had an enormous impact on the field of epilepsy surgery.

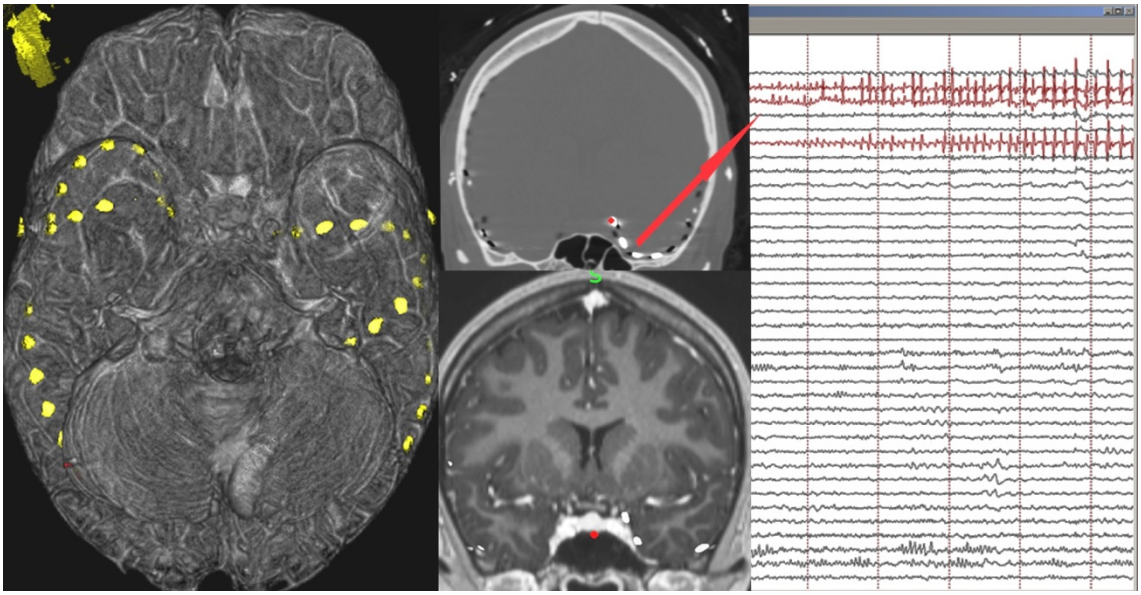
1.5 Epilepsy surgery today

The main objective of the pre-surgical evaluation is to identify the brain region that needs to be resected or disconnected to achieve the best chances for seizure freedom or seizure reduction (i.e. the epileptogenic zone), with minimization of risk of imposing new cognitive or neurological deficits. This basic concept has remained unchanged through the last decades, whereas the technical advances have contributed to major progress in the evaluation process. The cornerstones of the pre-surgical evaluation are i) a detailed history and semiology description indicating focal epilepsy, ii) video-EEG documenting ictal semiology and EEG changes and iii) neuroimaging, especially high resolution MRI where anatomical abnormalities that correlate to the suspected origin of seizures are sought. Neuropsychological assessment is mandatory in mapping cognitive abilities and deficits, both to establish baseline levels and to disclose cognitive deficits, which might have been caused by the epilepsy or the underlying aetiology. Psychiatric problems and vulnerability need to be carefully considered in the pre-surgical assessment. Patients must be optimally treated and have the capability to cooperate during the sometimes strenuous evaluation process. These investigations constitute the minimal pre-surgical evaluation set and may suffice to make a decision about whether to operate or not in straightforward cases. In non-lesional cases (negative MRI), or when MRI abnormalities are diffuse or uncertain, or when the localization is near eloquent areas (i.e. areas of vital functional importance), further non-invasive or invasive techniques are often required. Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) are non-invasive functional imaging methods for localization of the epileptogenic zone. ^{18}F-fluorodeoxyglucose

(^{18}FDG) PET is used to identify areas of hypometabolism which are sometimes found in focal epilepsy. SPECT is a technique which can be used to measure ictal and interictal blood flow. In SISCOM analysis, these images are subtracted and co-registered to MRI. Functional MRI (fMRI) can be used to localize or lateralize e.g. language functions or primary sensory or motor areas. Other non-invasive modalities for localization of the epileptogenic zone or identification of eloquent cortex include magnetoencephalography (MEG), spike-triggered fMRI, diffusion tensor imaging and transcranial magnetic stimulation.

Invasive techniques can be used for further localization of the epileptogenic zone. A prerequisite for the use of invasive techniques is a well-defined hypothesis regarding the localization of the epileptogenic zone, as the investigation must be planned to cover a predefined area or volume. Intracranial EEG recordings can be performed using subdural strip or grid electrodes (i.e. on the surface of the brain), intracerebral depth electrodes, or a combination of subdural and intracerebral electrodes (Figure 1). An increasingly used but demanding technique is stereo-EEG, where depth electrodes are placed stereotactically. The intracranial electrodes are very sensitive to interictal and ictal discharges, but also cover a very limited space and can easily fail to detect seizure activity if the underlying hypothesis is wrong. Electrocortical stimulation for mapping of eloquent cortex or eliciting habitual seizures can also be performed when invasive electrodes are used. The evidence for which ancillary techniques that should be used is very sparse.[20]

The abundance of technical modalities reflects the fact that localization or delineation of the epileptogenic zone may be very difficult. Also, the epileptogenic zone may be composed of circuits that are embedded into, or constitute parts of functional networks, imposing a major obstacle to surgery. Some of the investigational methods are surrogate markers and no findings guarantee that seizure freedom will follow surgery.



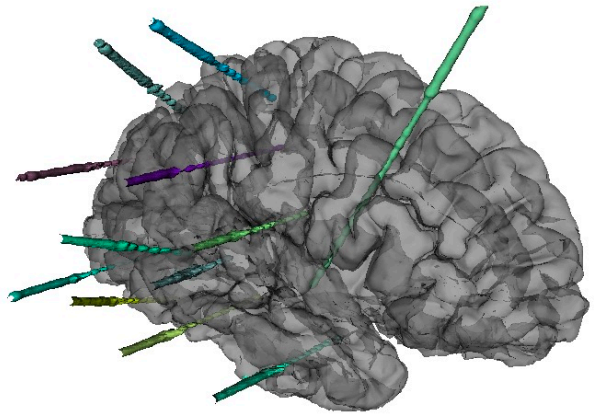


Figure 1.

Top: Subdural strip electrodes on MRI and CT images and corresponding EEG-recording. Electrode recordings with initial seizure activity are highlighted in red. Courtesy of prof. Bertil Rydenhag.

Left: 3D-reconstruction of brain surface and electrodes in a patient with right-sided temporo-parietal stereo-EEG implantation. Courtesy of Dr. David Krýsl.

Temporal lobe resection (TLR) is the most common type of surgery, especially in adults (Figure 2). Surgery in neocortical areas in the frontal lobe is more common in children than in adults, and the posterior lobes are more seldom the targets for surgery.[21] Very few adults undergo hemispherotomies.[22] The surgical approach in resections may either be excision of a defined lesion (lesionectomy), or resection of parenchyma where the surgical boundaries are either based on a standard approach (as in most cases of TLR) or defined from invasive pre-surgical EEG recordings and neuroimaging of anatomical structures.

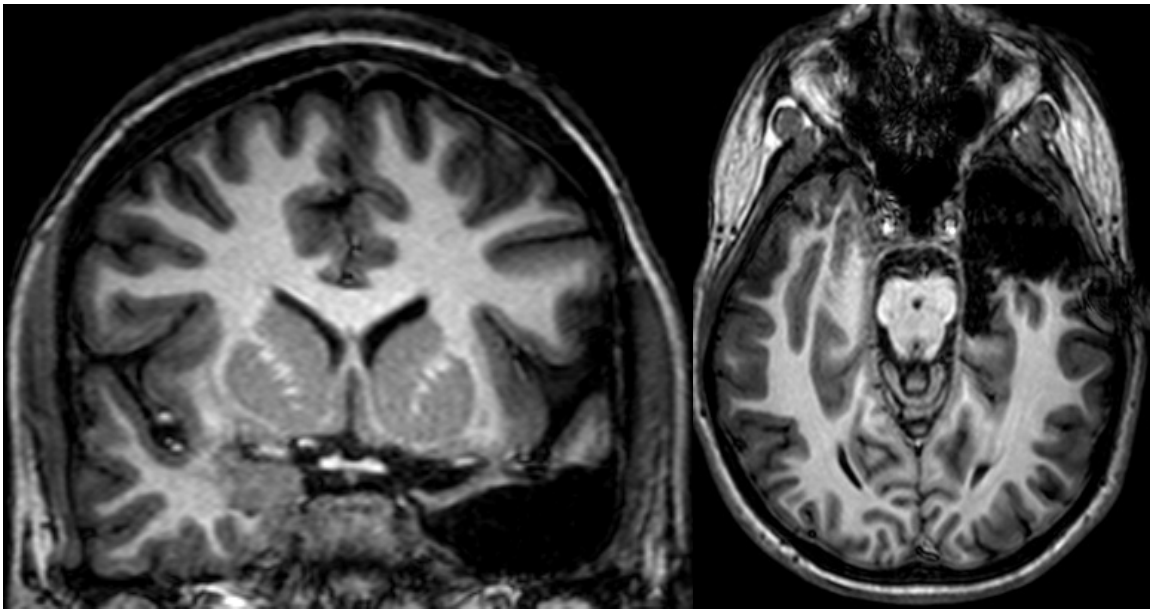


Figure 2. *Post-operative MRI of temporal lobe resection (TLR).*

In some cases resective surgery is not possible (typically in the case of widespread pathology) and non-resective surgery, with a palliative intention, might instead be an option. The most common non-resective procedure is the corpus callosotomy, which is sometimes a treatment option in patients with traumatizing drop attacks. In this case, the aim is not to abolish all seizures, but to prevent the fast spread of seizure activity, through partial or total division of the corpus callosum.[23]

2 Outcomes of epilepsy surgery

The most obvious goal of epilepsy surgery is achievement of seizure freedom, but patients also have expectations of other benefits like reduction of AEDs, improvements in employment and quality of life. Patients also want to know about the risk of adverse effects of surgery. Since long-term outcomes are the focus of this thesis, these will be dealt with more extensively in sections 4 and 5.

2.1 Short-term outcomes

There is Class I evidence for the short-term efficacy (one and two years follow-up, respectively) from two randomized controlled studies (RCTs) of temporal lobe resection (TLR) which is the most common surgical procedure in adults.[24, 25] The first of these studies (covering 80 patients) demonstrated seizure freedom in 64% of the operated patients (58% in the intention-to-treat surgical group) after one year, compared to 8% in the group with continued medical treatment.[24] In 2003, the American Academy of Neurology published a practice parameter after review of available evidence for temporal lobe surgery and localized neocortical resections.[17] The conclusion was that there was evidence for surgical treatment of mesial temporal lobe epilepsy (one RCT and 24 class IV studies), but insufficient evidence for neocortical resections, and that further research was warranted to investigate the possible benefit of early surgery. The primary aim of the multicentre RCT 'ERSET' was to investigate the effect of early surgical therapy for drug-resistant temporal lobe epilepsy (within two years of onset). However, this study was terminated early due to slow accrual, after randomization of only 38 patients to surgery or continued medication. At two-year follow-up, 11/15 surgical patients and 0/23 controls were seizure-free.[25] Results from studies with follow-up of one to five years have found freedom from disabling seizures in about two thirds of patients after TLR and in half after neocortical resections.[17, 26] There are no RCTs of frontal lobe resections (FLR), other extratemporal lobe resections, hemispherotomies or corpus callosotomy.

Wiebe and colleagues also reported on changes in AED treatment, quality of life and adverse events.[24] Awareness of possible adverse events is important in the counselling process before surgery.

2.2 Adverse effects

Neurological deficits

Every surgical procedure carries risks for haemorrhage and postoperative infections that may cause long-standing sequelae. Cortical resections also carry the risk of a neurological complication. Major surgical and neurological complications (defined as complications with lasting sequelae) occur in around 3% and minor complications (defined as complications that resolve completely within three months) occur in around 8% of cases.[27, 28] Complications of invasive investigations are usually minor and occur in 2-5% of patients, but include bleedings, venous cerebral ischaemia and infections.[29, 30] Surgery may not be possible if the location of the epileptogenic zone is in or near eloquent areas, e.g. primary visual or motor cortex, speech processing areas, or the pyramidal tracts. If surgery is planned in close proximity to such areas, there is always a higher risk for deficits. TLR poses a particular risk for contralateral upper quadrant visual field defect due to the course of the posterior part of the visual pathway. New imaging techniques, such as diffusion tensor imaging, are being used with the aim to minimize such expected defects by delineating the visual pathways in the individual patient.[31, 32] Hemispherotomy is usually performed in children with pre-existing hemi-dysfunction and may cause further impairment of hand function and vision.

For a few patients epilepsy surgery may not result in a lower seizure frequency. New seizure types, or altered seizure semiology (e.g. loss of aura) may occur, or seizure frequency may even be increased. Seizure worsening has been reported to occur in 1-8% of patients after surgery.[33]

Cognitive deficits

Medial temporal lobe resection (TLR) includes removal of the hippocampus. Hence, the most well documented cognitive adverse effect is impairment of memory functions, which is noted as a verbal memory decline in at least a third of patients after TLR on the language dominant side. Surgery on the non-dominant side has lower risks for memory impairment.[34-36] Neuropsychological assessment is one of the important pre-surgical investigational tools to explore dysfunctions that may have been caused by long-standing epilepsy. It may also predict the possible risks associated with the proposed surgical intervention. The degree of further memory decline after surgery has been shown to vary considerably between individuals.[37, 38] Patients with impairment of memory functions pre-operatively have less to lose and may be less affected by the worsening of memory functions than those with a well-functioning memory. On the other hand, if memory is already severely impaired, surgery might deprive the patient of the 'last important remnants' of memory function essential in everyday life. There are few studies of cognitive adverse effects after frontal lobe surgery.[39, 40]

Psychiatric adverse effects

Patients with a pre-operative history of psychiatric comorbidity, especially mood and personality disorders, have a higher vulnerability to develop depression and anxiety after surgery.[41, 42] The risk for this is lower if the patient becomes seizure-free. Some patients may also develop de novo psychiatric disease, most often mood disorders, but also psychosis.[43]

3 Pre-operative counselling

Patients with drug-resistant epilepsy who may benefit from surgery should be identified as early as possible, before the negative consequences of epilepsy become extensive.[44] The multidisciplinary pre-surgical evaluation process is time-consuming and demanding for the patients as well as costly for care givers. The severity of epilepsy is also an important determinant for surgery. The worse the epilepsy, the more willing the patients and the epilepsy surgery teams may be to accept lower chances of seizure freedom. However, brain surgery for epilepsy is an irrevocable procedure with risks and possibilities, but without guarantees of seizure freedom.

Patients or parents often need time to consider information and reach a decision for or against surgical treatment. The epilepsy surgery team should base the information to patients on as sound scientific grounds as possible, both when it comes to benefits and risks. Patients and their families need information not only about short-term outcomes, but also about long-term effects of epilepsy surgery on seizures as well as on other outcomes. Long-term studies are therefore important and can provide patients with the information they need in order to make well-informed decisions and to have realistic expectations.

4 Long-term outcomes: methodological aspects

4.1 General methodological considerations

The ultimate study design for outcome assessment of any treatment strategy, including surgery, is the randomized controlled study (RCT). This study design ensures that baseline characteristics are comparable in different treatment groups and accounts for the natural course of the disease. Long-term outcome studies of epilepsy surgery are by necessity observational since RCTs would be unfeasible as well as unethical. However, observational studies have methodological limitations that need to be considered when interpreting results and comparing studies. The three main types of observational studies are cohort studies, case-control studies and cross-sectional studies and they all have strengths and limitations. A number of quality criteria need to be taken into consideration when reading the literature and when designing observational studies. The following section will address some of these issues.[45, 46]

Studies should have a *prospective* design, with clearly defined *inclusion criteria*. A retrospective design mostly implies that baseline data are collected from medical records, and relies on completeness in these records. Also, retrospective studies are prone to include patients still being followed at the clinic at the time of inception in the study and may miss patients who have been lost to follow-up for several reasons (e.g. death, moved away, dissatisfaction with surgery). It is important to use *precise definitions* of variables, both for baseline variables, especially when predictors of outcome are investigated, and for the definition of outcome measures. The study cohort should be *representative* of the population and the possibility of referral or selection bias should be considered. The study centre might have a population which is not representative for the general epilepsy surgery population, thus reducing the generalizability of the results.

Virtually all outcomes after epilepsy surgery are subject to change depending on the *length of follow-up*, with the exception of surgical complications. With longer follow-up times, more patients will experience

seizure relapse, if only sometimes just one or a few seizures. Other outcomes, as for example number of AEDs, employment status and health-related quality of life (HRQOL) can be expected to change over subsequent years for a number of reasons. Such changes over time may be captured by using a *longitudinal* study design, with repeated follow-ups at set time intervals. If cross-sectional follow-up is used for outcome measures that change over time, it will be very difficult, if not impossible, to interpret the temporal changes. On the other hand, studies with long follow-up duration might have problems with high *drop-out* rates, which may bias the results towards a better outcome.

In epilepsy surgery studies *masking of outcome* is difficult. This might influence patients and investigators and give room for subjective interpretations of outcome. Well-defined outcome variables might minimize the effect of unmasking. *Large enough cohorts* are essential since small numbers of patients will weaken the reliability of the results. The change and development of *advanced technology* in pre-surgical evaluation has certainly had an impact on the selection of surgical candidates, but whether this leads to better long-term surgical outcomes remains to be proven.

Finally, the importance of adequate *statistical methods* is sometimes overlooked. Common mistakes include inappropriate use of parametric tests for non-normal distributed or categorical data, and improper methods used in predictive analyses.

The most studied and most evident outcome measure after epilepsy surgery is seizure outcome, but several other outcomes are important for the patient. The following section will specifically discuss the assessment of the outcomes studied in this thesis: seizures, use of AEDs, employment and health-related quality of life (HRQOL). Aspects not further considered (despite their obvious importance) include complications, cognitive and psychiatric outcomes, and psychosocial outcomes other than employment status.

4.2 Seizure outcome

Comparisons between studies assessing seizure outcome are made difficult by the lack of consistent definitions. The most commonly used scheme is the Engel classification with one original (1987) and one revised version (1993), shown in text boxes below.[47, 48] Seizure freedom is classified as Engel I, and sub-class I A refers to those completely seizure-free since surgery. In the original version, class I B identifies patients who have had auras only but no other seizures since surgery, while the more commonly used revised version accepts all non-disabling simple partial seizures (including focal motor seizures without impairment of consciousness). The ambiguity of concepts such as 'disabling', 'rare seizures' and 'worthwhile improvement', where there is room for subjective interpretation, has been criticized. Objections have also been raised to using numbers of seizures rather than seizure days when determining change in seizure frequency. This critique of the Engel classification led to the development of the International League Against Epilepsy (ILAE) outcome scale.[49] While some categories in the Engel classification take the whole postoperative period into account, the ILAE classification refers to seizure outcome the last year before follow-up and advocates that seizure outcome should be reported at annual intervals after surgery. However, the two classifications have in common the possibility to identify patients who have been completely seizure free without aura since surgery (Engel class I A, and ILAE class 1a). Both the Engel and the ILAE classifications exclude early postoperative seizures (first few weeks for Engel and first month for ILAE).

The ILAE classification has no class for seizure-free with aura since surgery. Other issues not addressed by the ILAE classification are seizure severity or change in frequency of different seizure types for those not seizure-free. The Engel classification, on the other hand, is dependent on the subjective definition of 'disabling' and 'worthwhile improvement'. Although both scales include a possibility to note worsening of seizure frequency postoperatively, this is seldom reported.

Engel classification 1987:

Class I: Seizure-free[a]
A. Completely seizure-free since surgery
B. Aura only since surgery
C. Some seizures after surgery, but seizure-free for at least 2 years
D. Atypical generalized convulsions with antiepileptic drug withdrawal only

Class II: Rare seizures ("almost seizure-free")
A. Initially seizure-free but has rare seizures now
B. Rare seizures since surgery
C. More than rare seizures after surgery, but rare seizures for at least 2 years
D. Nocturnal seizures only, which cause no disability

Class III: Worthwhile improvement
A. Worthwhile seizure reduction
B. Prolonged seizure-free intervals amounting to greater than half the follow-up period, but not less than 2 years

Class IV: No worthwhile improvement
A. Significant seizure reduction
B. No appreciable change
C. Seizures worse

[a]Excludes early postoperative seizures (first few weeks)

Engel classification 1993:

Class I: Free of disabling seizures[a]
A. Completely seizure-free since surgery
B. Nondisabling simple partial seizures only since surgery
C. Some disabling seizures after surgery, but free of disabling seizures for at least 2 years
D. Generalized convulsion with antiepileptic drug withdrawal only

Class II: Rare disabling seizures ("almost seizure free")
A. Initially free of disabling seizures but has rare seizures now
B. Rare disabling seizures since surgery
C. More than rare disabling seizures after surgery, but rare seizures for at least 2 years
D. Nocturnal seizures only

Class III: Worthwhile improvement[b]
A. Worthwhile seizure reduction
B. Prolonged seizure-free intervals amounting to greater than half the follow-up period, but not less than 2 years

Class IV: No worthwhile improvement[b]
A. Significant seizure reduction
B. No appreciable change
C. Seizures worse

[a]Excludes early postoperative seizures (first few weeks).
[b]Determination of "worthwhile improvement" will require quantitative analyses of additional data such as percent seizure reduction, cognitive function, and quality of life.

ILAE classification 2001:

Class 1. Completely seizure free; no auras
Class 1a. Completely seizure free since surgery; no auras
Class 2. Only auras; no other seizures
Class 3. One to three seizure days per year; ± auras
Class 4. Four seizure days per year to 50% reduction of baseline seizure days; ± auras
Class 5. Less than 50% reduction of baseline seizure days to 100% increase of baseline seizure days; ± auras
Class 6. More than 100% increase of baseline seizure days; ± auras

Seizure freedom is mostly defined either as Engel I A, Engel I A+B, ILAE 1+2 or Engel I. Seizure outcome is often reported for the year preceding follow-up, without reporting separately those who have been seizure-free since surgery. Studies of seizure outcome often illustrate seizure-free survival using Kaplan-Meier curves, which is appropriate for Engel class I A or Engel I A+B, but not for Engel I. Engel I C, which denotes patients with postoperative seizures but who are seizure-free during the last two years, is particularly problematic when included in survival analyses.

4.3 Antiepileptic drug treatment

AED outcomes vary widely across studies and are mostly reported as proportion of patients using zero, one, two or more AEDs. Sometimes AEDs are reported for all operated patients, sometimes only for those seizure-free. Some authors report the relapse rate in those where AED reduction is attempted. The reduction of drug load is seldom addressed. Furthermore, AED outcome is highly dependent on the follow-up period, and cross-sectional reports will only provide a crude mean and fail to illustrate the presumed gradual decrease over time. Implications of continued AED medication are different for children and adults, and AED outcomes should be reported separately for children and adults.

4.4 Vocational outcome

Individuals with epilepsy have higher levels of unemployment and underemployment than people in general.[50] Underemployment refers to when a person is working fewer hours, or in positions with lower levels of skills and experience than expected or desired, based on his or her qualifications. Employment outcome after epilepsy surgery is often reported as part of other psychosocial outcomes, and most reports concern TLR patients only.[51] Cross-sectional studies of patients with a wide range of follow-up times will fail to illustrate dynamic changes that occur over longer periods of time. Studies including patients with an age span from early adulthood to middle-age, with widely differing employment perspectives, may not provide an appropriate description of employment

outcome, if reported only at group level. Several factors besides seizure outcome influence employment and need to be considered. Individual variables such as employment status before surgery, age at surgery, educational level, cognitive function, mental health and other comorbidities as well as societal factors, such as socioeconomic systems and availability of employment, are aspects that should be addressed. Furthermore, the varying definitions used for seizure freedom can make it difficult to compare results across studies.

4.5 Health-related quality of life

The concept of health-related quality of life (HRQOL) reflects the impact that illness imposes on how people experience their lives and how illness affects overall well-being and daily functioning. This is a difficult-to-define area of knowledge, but can be divided into physical health (e.g. general health, symptoms of illness such as seizures and pain, side-effects from drugs etc.), mental health (e.g. mood, self-esteem, perceived stigma) and social health (e.g. social activities and relationships).[52] Drug resistant epilepsy imposes many restrictions on daily living, including risk of injuries, side-effects from medication, embarrassment of having seizures 'in the wrong situations' and restrictions on driving.

HRQOL is often assessed through validated surveys. These can be generic or disease specific, or a combination of the two. Generic instruments assess a range of domains and well-being and can be used for many different diseases and conditions. Disease specific instruments often include a generic core and in addition disease-specific areas are covered, e.g. the Quality of Life in Epilepsy Inventory (QOLIE-89)[53] or the Epilepsy Surgery Inventory (ESI-55).[54] Generic and disease specific instruments have their respective strengths and weaknesses. While epilepsy specific HRQOL instruments are more sensitive to change,[55, 56] the use of generic instruments enables comparisons both with the general population, and with cohorts with other chronic diseases.[57] The 36-item Short Form Health Survey (SF-36) is a widely used generic instrument with high reliability and large norm reference populations. It has repeatedly been shown to be a sensitive instrument also in epilepsy populations.[58] The Swedish norm

reference database contains data from almost 9,000 persons, enabling comparison with a matched reference population.[59]

Changes in HRQOL scores are dependent on the type of questions and the scoring system within the instrument. To appreciate the meaning of score changes, they need to be related to other variables or circumstances in patients' lives, such as gaining or losing employment, being able to drive, degree of social independence etc.[60] Research in this field has resulted in establishment of levels for 'minimum clinically important difference' (MCID) for several HRQOL instruments. MCID has been found to vary depending on disease and cut-off values have been established in epilepsy populations for QOLIE-89 and for the physical and mental component summaries (PCS and MCS) of SF-36.[61]

5 Long-term outcomes: literature review

5.1 Seizure outcome

Seizure outcome is the most studied outcome of epilepsy surgery. In a meta-analysis from 2005 based on 78 long-term follow-up studies, 66% of TLR patients, 46 % of patients who had parietal or occipital resections and 27% of frontal lobe resection (FLR) patients were seizure-free at follow-up after a minimum of five years. However, the authors point out that most reported seizure status during the year preceding follow-up, and few studies reported sustained seizure freedom from surgery. In addition, most studies had a cross-sectional design, making it difficult to identify temporal patterns. Almost all studies described patient cohorts without controls.[21]

Several long-term seizure outcome reports have been published in recent years for a variety of surgical interventions. Considering the methodological issues discussed above, longitudinal studies with good methodology have been summarized in Table 1 at the end of this section. To facilitate interpretation of the results, studies are ordered according to seizure outcome assessment. Studies with the strictest definition of seizure freedom are listed first (Engel I A or ILAE class 1a), and seizure-free ± auras last year of follow-up (ILAE classes 1 and 2) last. Furthermore, studies reporting outcomes after FLR and other extratemporal resections are placed at the very end of the table.

More recent studies with prospectively collected long-term data on seizure outcome have provided better information about the chances of sustained seizure freedom since surgery. The largest of these, which is a single-centre study of 1160 patients (adults and children) with a mean cross-sectional follow-up of 5.4 years (range 2.0-20.5 years), found that 50.5% were seizure-free without auras since surgery.[62] In a study from UK ('the UCL study') with longitudinal yearly follow-ups of 615 adults, 52% remained seizure-free (apart from seizures without impairment of consciousness) five years after surgery and 47% at 10 year follow-up.[63]

Seizure outcome after temporal lobe resections

TLR constitute 70-80% of resective epilepsy surgery procedures in adults and there are many single-centre seizure outcome reports of TLR. Seizure-free outcomes five years after surgery vary considerably, from 46% to 91%, largely depending on outcome definitions, inclusion criteria and study design. A number of longitudinal long-term studies report sustained seizure freedom after TLR. Most are retrospective single-centre series, and only a few are prospective. Seizure freedom is reported as Engel I A,[64, 65] Engel I A and B,[66] ILAE class 1 and 2,[63, 67] or Engel I.[68, 69] The proportion of patients with sustained seizure freedom five years after surgery is reported to be between 46% and 80%.[63, 64, 66-68, 70, 71] Prospective studies generally report lower rates of seizure freedom. All studies showing higher rates of seizure freedom except one were retrospective and mostly used the category Engel class I. A few studies report longitudinal follow-up up to 10 years post-surgery. In one retrospective single-centre study of 325 patients (adults and children), 48% had sustained seizure freedom (defined as Engel I A, B and D) after five years and 41% after 10 years.[69] In the UCL study, 55% of 497 TLR patients remained free from seizures, without or with auras, five years and 49% 10 years after surgery.[63]

Studies in children mostly have cross-sectional long-term follow-ups, reporting seizure freedom in 50-82% of patients 5-12 years after TLR.[72-75] Only one study is longitudinal and reports sustained seizure freedom in 54% of patients five years after TLR.[76]

Seizure outcome after frontal lobe and other extratemporal resections

A systematic review of long-term outcomes after FLR published 2012 included 21 articles (adults and children) with a mean or median follow-up of at least four years.[77] All studies were single-centre retrospective or prospective series and the seizure-free rates at long-term varied from 20% to 78%. The overall rate of postoperative seizure freedom reported as Engel I was 45%. Only two studies provided longitudinal data, and seizure outcome at five years (Engel I) were 27% and 47%, respectively.[78, 79]

Some more recent studies of long-term outcomes after FLR or other extratemporal resections provide information on sustained seizure

freedom since surgery. In one prospective study with a minimum follow-up of five years, 15% had sustained seizure freedom (Engel class I A+B) at five years.[70] In another cross-sectional FLR study with a mean follow-up of six years (range 1-17 years) 24% were reported to have sustained seizure freedom (Engel I A).[80] One study of extratemporal surgery reported Engel I outcome in 55% and Engel I A in 37% at five-year follow-up.[81] The diverging long-term seizure outcomes after extratemporal resections may partly be attributable to varying histopathological diagnoses. Studies reporting higher rates of seizure freedom generally include a larger proportion of patients with well-defined lesions, see below.[82]

Seizure outcome is related to histopathology

The differences in seizure freedom rates for TLR and extratemporal resections are partly due to histopathology. Hippocampal sclerosis is the most common histopathology in adult TLR patients. In this group of patients, around 50% have sustained seizure freedom since surgery after five years and 65-80% have seizure freedom during of the year preceding follow-up.[64, 67, 83] Patients with well-defined lesions, such as glioneuronal tumours (i.e. gangliogliomas and dysembryoplastic neuroepithelial tumours) and cavernomas have better seizure outcome than those with diffuse or wide-spread anomalies. Long-term seizure freedom rates in patients with lesions have been found to be 75-80%,[81, 84, 85] which is similar to short-term outcomes.[86, 87] For focal cortical dysplasia (FCD) outcomes are not consistent. One recent large longitudinal study found that 64% of patients had Engel I and 53% Engel IA outcome five years after surgery, with no difference between FCD subtypes.[88] Other investigators report more modest outcomes, with the lowest seizure freedom rates in FCD type I.[70, 81] Focal cortical dysplasias may have parts not visible on MRI, and the radicality of surgery may be difficult to evaluate. Seizure outcome results can vary, partly due to subtotal resection, or to a previously non-homogenous classification, but lately the classification has been more precisely defined.[89] These factors may contribute to variations in outcome.

Seizure outcome is not a static condition

Seizure outcome for surgically or medically treated patients is not constant. The changing patterns of seizure control over time complicate the evaluation of outcome. Most relapses after surgery occur in the first two to three years, after which new relapses become less frequent. Figure 3 illustrates data from three large centres, describing time to first seizure in adult patients after TLR with a histopathological diagnosis of hippocampal sclerosis. Although the time periods differ and the cohorts may be different in other aspects, the pattern of relapse is remarkably consistent.

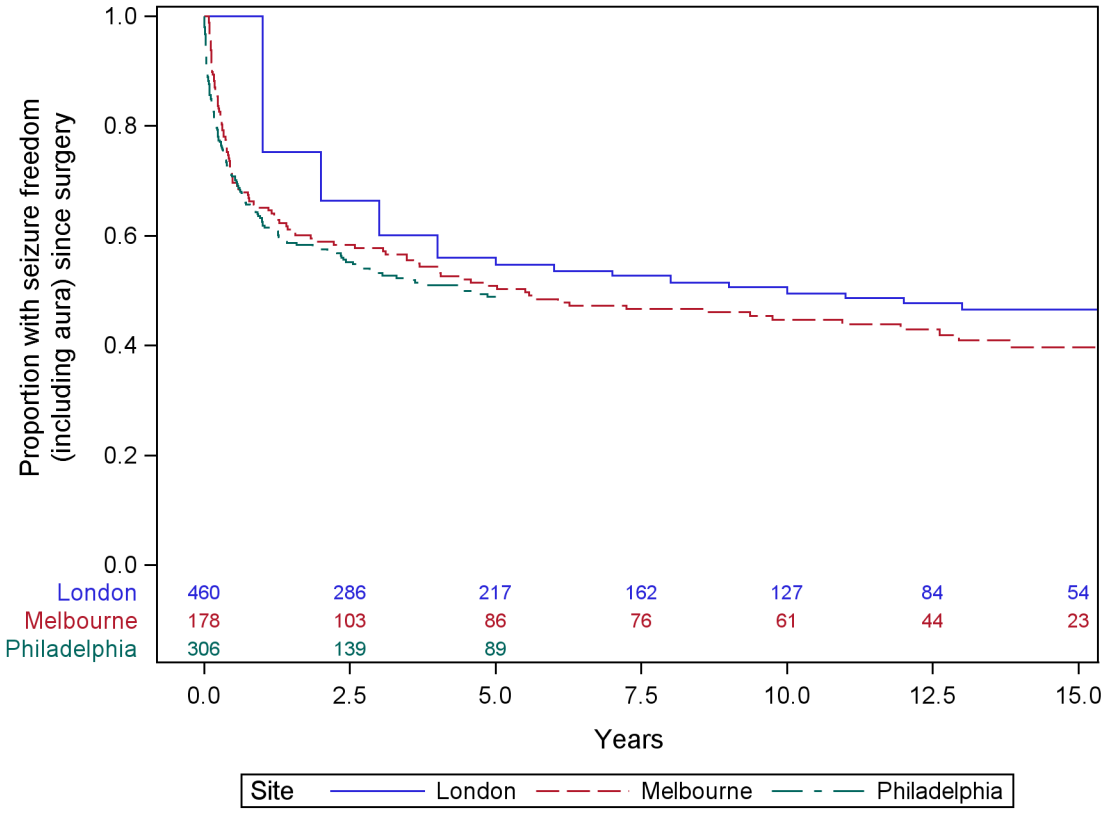


Figure 3. *Kaplan-Meier curve for sustained seizure freedom (allowing auras) after temporal lobe resection for hippocampal sclerosis. Data from three large epilepsy surgery centres: Austin Health, Melbourne, Australia (enrolled 1979-1998, courtesy of Drs A. McIntosh and S. Berkovic), Jefferson Comprehensive Epilepsy Centre, Philadelphia, USA (1987-2014, courtesy of Drs A. Asadi-Pooya and M. Sperling) and UCL, London, UK (1990-2008, courtesy of Dr J.S. Duncan). The data from UCL were collected annually after surgery, hence the step-wise appearance of the curve. (Reprinted with permission from Springer: Eds Malmgren et al, Long-term Outcomes of Epilepsy Surgery in Adults and Children, Springer, Switzerland 2015, Malmgren et al,[90] Fig 3.1)*

A retrospective study of 175 patients who had been seizure-free for one year after resective epilepsy surgery, found that 63% never relapsed during a mean follow-up of 8.3 years. The likelihood of remaining seizure-free declined to 56% over a period of 10 years, but half of the patients who relapsed had no more than one seizure per year.[91] In another study of 285 patients with one year of postoperative seizure freedom, 18% had relapsed by five years and 33% by 10 years.[92] The prospective 'US Multicenter study' with a longitudinal follow-up of 339 patients found that of 223 patients, who at some point during follow-up (2-7 years) had entered a two-year remission, 25% had seizure relapse later. Patients who entered a two-year remission immediately after surgery were less likely to relapse later than those who had a two-year remission at a later time.[26] In the UCL study with longitudinal follow-ups annually up to 17 years post-surgery, 68-73% had been seizure-free (or had only focal seizures without impairment of consciousness) the year preceding follow-up. This proportion was stable, although at an individual level many had sporadic relapses. Patients who were seizure-free two years after surgery had an 80% chance of still being seizure-free after another five years, and those with sustained seizure freedom five years postoperatively had an 89% chance of still being seizure free after 10 years.[63]

Predictors of long-term seizure outcomes

Several studies have investigated predictors for seizure outcome at long-term (at least four years), with varying results. Common identified predictors for seizure freedom are positive MRI and histopathology (varying depending on types of pathology included in analysis).[63, 68-70, 79, 84, 93] Positive predictors in patients after FLR were lesional epilepsy, abnormal MRI and localized resection as opposed to more extensive frontal or multilobar resections.[77] There are also studies where no factors remained predictive in multivariate analysis.[64, 67, 80]

Predictors for long-term outcome seizure recurrence have also been identified and include the following: generalized convulsive seizures at baseline,[26, 69, 92] long epilepsy duration,[62, 84, 94-96] higher age at surgery,[63, 82, 88, 92] high baseline seizure frequency,[97] postoperative interictal epileptiform discharges[65, 93, 94] and early postoperative seizures.[70, 79, 98]

5.2 Antiepileptic drug treatment

The proportion of seizure-free adults and children in whom AEDs have been discontinued after epilepsy surgery varies widely across studies. A Canadian survey on AED management after successful epilepsy surgery showed that epileptologists had diverging opinions on the optimal timing of withdrawal and reasons for or against such a decision.[99] There is no consensus regarding management of AEDs after successful epilepsy surgery and no systematic studies of the optimal timing of postoperative drug withdrawal in adults.[100] A large retrospective pan-European study of AED outcome in children investigated seizure recurrence as a function of timing of AED tapering.[101] The main conclusion was that long-term seizure outcome was not affected by early withdrawal, but that the 'true surgical result' was uncovered earlier and that seizure relapse only happened in those where continued AED treatment was necessary. After AED withdrawal, 45% of children achieved at least one year of seizure freedom without medication.

Side effects of AEDs contribute to poor quality of life,[15] and many patients have expectations to withdraw AEDs after successful surgery.[102-104] On the other hand, adult patients have many aspects to consider when deciding for or against AED discontinuation, not least the psychosocial consequences of seizure recurrence with regard to occupational abilities and driving. The way information about risks is presented to patients influences their decisions,[105] and in one study where a computer-based predictive model was used for counselling medically treated seizure-free patients about individualized recurrence risks, the majority decided to continue AEDs.[106] Framing of information may be one reason for the varying results in different studies. In children, the negative effects of AEDs on cognitive development are a strong incentive for early reduction of AEDs.

In a meta-analysis of AED outcomes from 2007, nine studies were identified. A pooled analysis showed that only 19% of seizure-free adults and 27% of children had discontinued AEDs at a mean follow-up of seven years.[107] The UCL study reported that 28% of seizure-free patients (mostly adults) were without AEDs at last follow-up (median eight years),[63] and similar results have been reported after neocortical resections: 27% of seizure-free had ceased AEDs after a median of seven years.[108] A more

recent study with a mean follow-up of 4.6 years after TLR reported that 19% of all adult patients had discontinued AEDs.[109] In all of these studies, AED outcome was reported cross-sectionally. In a longer study with mean follow-up 12.4 years (range 8.6-16.2), 29% of seizure-free adults had ceased AED therapy.[110] One longitudinal study reported that 55% of seizure-free children had stopped AEDs five years after surgery.[111]

Early withdrawal of AEDs has been studied after TLR and extratemporal resections in two Indian studies. For patients with two or more AEDs, pre-planned tapering was started after a seizure-free period of three months, and for those with only one AED, after one year of seizure freedom. AED withdrawal was successful in 63% after TLR (mean follow-up 8 years),[93] and in 28% after extratemporal resections (mean follow-up 4.6 years).[94]

A systematic review from 2012 identified nine studies investigating withdrawal of AEDs in seizure-free patients and reported the average recurrence rate to be 31%, with a range of 12-53% in individual studies.[112] A meta-analysis of seizure outcome after AED reduction versus no reduction found a lower risk of seizure relapse in those where AED reduction was attempted compared to those who continued medication (OR 0.4).[113] This seemingly paradoxical finding was interpreted to reflect the different risk profiles of these two groups of patients; AED reduction is more often attempted in patients where the risk profile for relapse is more favourable. Another meta-analysis investigating cumulative seizure relapse rates after initiation of postoperative AED reduction, found relapses in 14% at one year, 21% at two, and 29% at five or more years.[114] Common predictors could not be identified.

5.3 Vocational outcome

One of the most common desires among patients waiting to undergo epilepsy surgery is improved working capability. Knowledge about employment outcomes is very important, not only for the patient but also from a health economic perspective.[115, 116] Long-term studies of employment after epilepsy surgery show inconsistent results. Some investigators have found no change in the number of employed patients after surgery,[80, 116-119] while others have reported an increase in employment of 10-40%.[120-124] Two studies found a decrease in employment,

particularly for those not seizure-free.[110,125] The US Multicenter study found minor changes in the whole cohort, but 25 % of those who were disabled or unemployed before surgery were employed two years after surgery and this was associated with better seizure outcome.[116] Especially for those unemployed before surgery, it can take more than two years to find work.[120]

One US study from Philadelphia found an increase in full-time employment from 44% to 52% and a decrease in unemployment from 36% to 22%.[122] In contrast, a study from Detroit with similar cohorts and follow-up times, found a decrease in full-time employment from 42% to 23%.[125] Education, social support from family and friends, cognitive function, ability to drive and mental health are factors that are likely to influence employment after surgery. No study has compared employment outcome after epilepsy surgery to that of the general population.

Seizure outcome has repeatedly been identified as the most important factor affecting postsurgical employment, but results are not consistent.[51, 126] Other positive predictors of postoperative employment are younger age at surgery,[119, 120, 122, 127] higher IQ,[127, 128] shorter epilepsy duration,[119, 128] being a student or working full-time the year before surgery,[118, 122, 129] driving after surgery,[64, 118, 122] obtaining further education after surgery[118] and absence of personality disorder.[127] Importantly, vocational rehabilitation after surgery was found to be associated with postoperative employment in one study.[127]

5.4 Health-related quality of life

Health-related quality of life (HRQOL) is often affected in people with epilepsy. The unpredictability of seizures, risk of injuries, side effects of AEDs, stigma, implications for driving, lower employment rates and lower self-esteem are some of the important underlying factors. In a large European study of 5,000 persons with epilepsy, more than a third had frequent seizures and almost 90% suffered from side effects of AEDs.[130] Many felt that epilepsy had a negative impact on their feelings about themselves, social life, employment, standards of living and ambitions for the future.

HRQOL studies after epilepsy surgery are scarce and most have short-term follow-ups (one to two years) or examine patients at a single point of time without comparison to preoperative levels. Some have control groups for comparison. Comparison between studies is complicated by the use of different HRQOL instruments. Most studies have found an improvement in HRQOL after surgery, the major determinant for this being seizure freedom.[131] The US Multicenter study with annual assessments up to five years post-surgery found an increase in HRQOL scores within the first six months for all seizure outcome groups. After that HRQOL changes were related to seizure outcome. In seizure-free patients, HRQOL continued to improve up to two years after surgery, but after that the effect was attenuated. Patients who did not become seizure-free after surgery declined gradually to pre-surgical levels after the initial improvement. At five years, SF-36 scores of the seizure-free patients were compared to an age and sex matched population sample. Patients reached the same levels as norm on all domains except Social Functioning.[132] Worsening of HRQOL was seen for those with persistent seizures and verbal memory decline.[133] Further analyses of this cohort identified a strong relationship between depression and anxiety and low HRQOL, independent of seizure outcome.[134] Depression has repeatedly been found to be a major determinant of HRQOL in persons with epilepsy, more so in patients with persistent seizures than in seizure-free.[135]

A few HRQOL studies have compared TLR patients to controls waiting to undergo surgery, with consistent results of higher HRQOL scores in the operated patients.[136-139] One controlled long-term follow-up study (mean 8 years, range 5-11 years) of patients with temporal lobe epilepsy found significant improvement in the surgical group in overall, mental and physical subscales of the QOLIE-89 and unchanged scores in the medically treated control group. Comparison of seizure-free and not seizure-free patients resulted in even larger differences on all subscales.[140]

Only two studies have used minimum clinically important difference (MCID) in assessing HRQOL change after epilepsy surgery. One of these studies was an RCT of TLR with a follow-up of one year. After six months, 56% in the surgical group and 11% in the medical control group had improvements reaching MCID in overall HRQOL using the QOLIE-89. Worsening was seen in 8% of the surgical patients and 15% of the medical

patients.[141] The other study was a Swedish follow-up of epilepsy surgery candidates, where the non-operated group served as controls. Two years after surgery or pre-surgical investigation, operated seizure-free patients reached norm levels on all SF-36 domains except Social Functioning. In the surgical group, 45% of seizure-free patients reached MCID for mental component summary, versus 28% of not seizure-free and 29% of non-operated.[142]

Determinants of quality of life after surgery depend on which variables that have been investigated.[131] Most studies with control groups or repeated HRQOL assessments for surgical patients have found that epilepsy surgery in itself is a positive determinant of HRQOL. Preoperative factors that have been identified as predictors for worsening of HRQOL are poor psychological functioning, psychiatric comorbidity and unmet or unrealistic expectations. Seizure outcome has been identified as the most important predictor in almost all studies. The largest effects have been on psychosocial, physical, epilepsy-targeted domains and overall quality of life, less often on role-limitation and cognitive domains. However, one study found that pre-operative HRQOL was more predictive of post-operative HRQOL than seizure freedom.[143] Other postoperative predictors for improved HRQOL are employment, patient satisfaction and ability to drive.[131, 137] Negative predictors include adverse effects of AEDs, poor psychological function, verbal memory decline, physical comorbidities and seizure severity.[136, 137, 144]

Table 1. Well conducted longitudinal long-term seizure outcome studies

Author, year	Study design	Number in study group	Type of surgery	Lesion type (histology)	Outcome measure	5 year outcome %	10 year outcome %
Aull-Watschinger, 2008	R S L	72	RES, T	HS	ILAE 1a ILAE 1+2	46 79	
Fauser, 2015	R S L	211, ~97 at 5 years	RES, T+XT	FCD	Engel IA Engel I	53 64	
de Tisi, 2011	P/R S L	615 in cohort, 234 at 5 years, 122 at 10 years	All (but only 7 NRES)	All	ILAE 1+2 sustained, i.e. only SPS since surgery	52	47
Paglioli, 2004	P S L	135, 69 at 5 years	RES, T	HS only, no dual pathology	Engel I A Engel I	74 91	
McIntosh, 2004	R S L	138 at 5 years, 56 at 10 years	RES, T	All	Engel I A+B+D	48	41
Spencer, 2005	P M X	339	RES, T+XT	All	At least two years seizure remission, allowing auras	69	
Elsharkawy, 2009	R S L	419 at 5 years, 366 at 10 years	RES, T	All	Engel I	71	71
Sperling, 1996	R S L	89	RES,T	All	At least one year seizure remission, allowing auras	70	

Asztely, 2007	P S X	65	RES, T+XT	All	ILAE 1+2		58
Luyken, 2003	R S C	180 at 5 years, 67 at 10 years	RES, T+XT	Tumours	Engel I	81	81
Jeha, 2007	R S L	22 at 5 years	RES, F	All	Engel I	27	
Elsharkawy, 2008	R S L	66 at 5 years, 31 at 10 years	RES, F	All	Engel I A Engel I	35 47	35 42
McIntosh, 2012	R S L	81	RES, XT	All	Engel I A+B ILAE 1+2	14 37	

Abbreviations:

Study design P: prospective, R: retrospective, S: single-centre, N: national (population based), M: multicentre, X: cross-sectional, L: longitudinal

Type of surgery RES: resective surgery, NRES: non-resective surgery, T: temporal lobe, XT: extra-temporal lobes, F: frontal lobe

Lesion type HS: hippocampal sclerosis, FCD: focal cortical dysplasia

Outcome measure Sustained: continuous seizure freedom since surgery, SPS: simple partial seizures

6 Aims

Epilepsy surgery is a highly specialized treatment option for a limited number of patients with medically refractory epilepsy. The majority of patients are young with most of their lives ahead of them. Patients want to know what can be expected not only a few years after surgery, but in a much longer perspective. We need to explore the long-term effects of epilepsy surgery in order to give patients individualized pre-operative counselling and help them adopt realistic expectations.

The general aim of this study was to investigate long-term outcomes of resective epilepsy surgery in population-based cohorts of patients using a prospective and longitudinal methodology. The more specific aims were to:

I. Investigate seizure and antiepileptic medication outcomes at five and 10 years after resective epilepsy surgery and compare these to a non-operated control group (Study I).
II. Investigate employment outcomes at 5, 10 and 15 years after surgery, relate these to seizure outcome and compare the results with employment in the general population (Study II).
III. Identify predictors for good seizure outcome (Study I) and employment (Study II).
IV. Explore HRQOL and mood at long-term in surgically and medically treated patients and compare HRQOL levels to those of the general population (Study III).

7 Patients and methods

7.1 Study designs

Study I and II were prospective, population-based, longitudinal studies based on the Swedish National Epilepsy Surgery Register (SNESUR). SNESUR was initiated in 1990 by the National Board of Health and Welfare as a quality control register, where all six epilepsy surgery centres in Sweden participate (Lund, Göteborg, Linköping, Stockholm, Uppsala, Umeå). Inclusion in the register is fully prospective since 1995, and patients undergoing epilepsy surgery (not including vagal nerve stimulation) or invasive EEG recordings are reported during pre-surgical evaluation or at the time of surgery. Information is collected longitudinally for each patient at baseline and follow-ups. Baseline data comprise information on epilepsy history, seizure types and mean monthly frequency the year preceding the pre-surgical investigation, AEDs, psychosocial data, pre-operative investigations, and surgical data including type of surgery, location, histopathology and complications. Psychosocial data include information on education, employment, social security status, and family and living circumstances. Two-year follow-up data are collected at in-patient stays or hospital visits and cover seizure situation, AEDs and psychosocial data. The long-term follow-ups, initiated in 2005, are performed every fifth year as structured telephone interviews covering the same data as in the two-year follow-up. Hence, there is five-year and longer follow-up data for patients operated from 2000 and onwards, and 10-year and longer follow-up data for patients operated since 1995. The follow-ups of the cohorts in the three studies are shown in Figure 4.

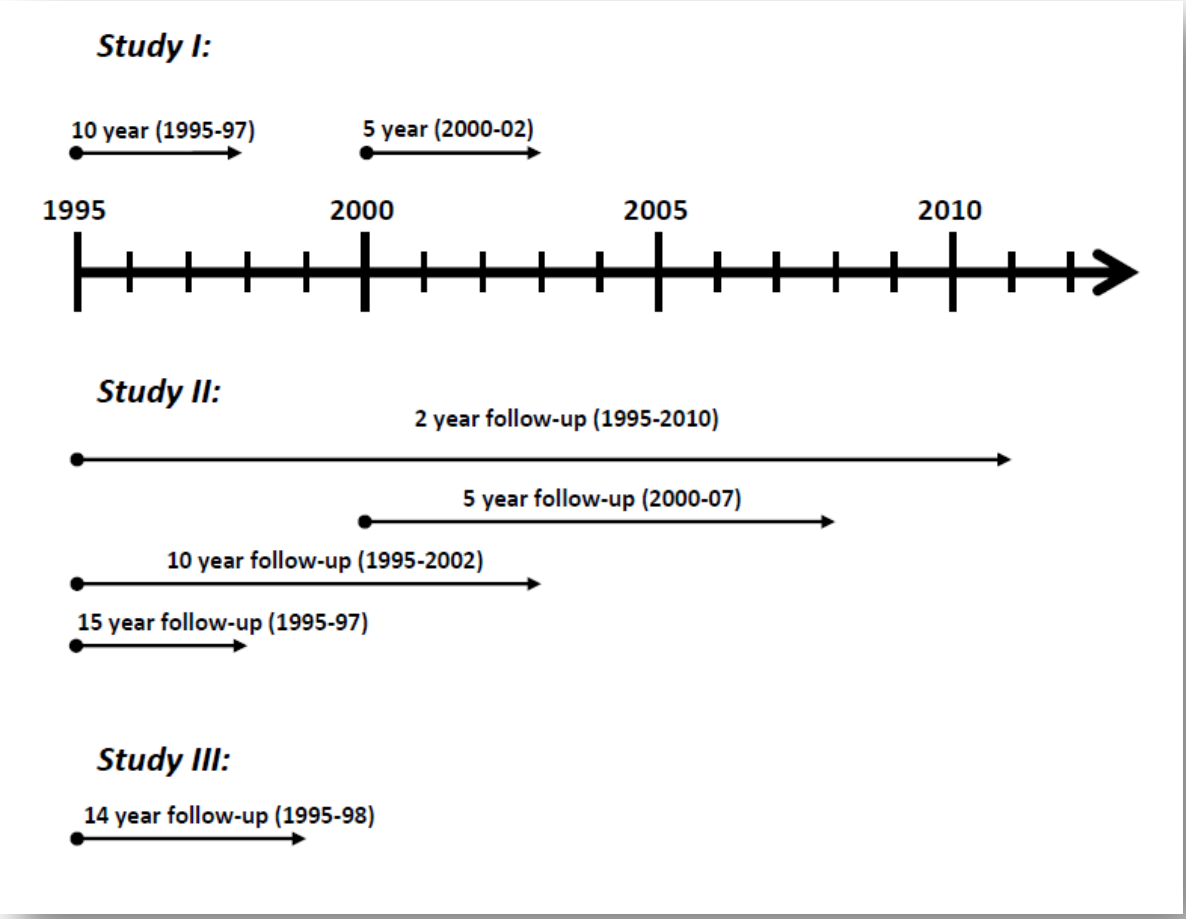


Figure 4. *Time-line illustrating the time periods for pre-surgical investigations and epilepsy surgery in the three studies.*

In *Study I*, seizure outcome and AED medication were analysed for patients who had resective surgery in 1995-1997 (with 10-year follow-up) and in 2000-2002 (five-year follow-up). The cohort consisted of 176 patients (116 adults, 60 children) operated 1995-1997 and 151 (103 adults, 48 children) operated 2000-2002. Ten-year follow-up was available for 144 patients (98 adults, 46 children) and five-year follow-up for 134 (92 adults and 42 children). See Figure 5 A for number of deaths and re-operations. Twenty-one patients (6.4%) were lost to follow-up. Consecutive patients who underwent epilepsy surgery evaluations during the same time periods, but were not operated for various reasons, served as controls. This group was not a national sample, but came from the three largest of the six surgical centres (Göteborg, Uppsala, Lund) where baseline data had been

prospectively collected during pre-surgical evaluation. Of the 107 identified patients (94 adults, 13 children), 80 adults and 13 children underwent a cross-sectional follow-up using the same telephone interview as the surgical patients, after a mean of 9.3 years (adults, range 5-14), and 8.8 years (children, range 7-13). There was no two-year follow-up for the controls.

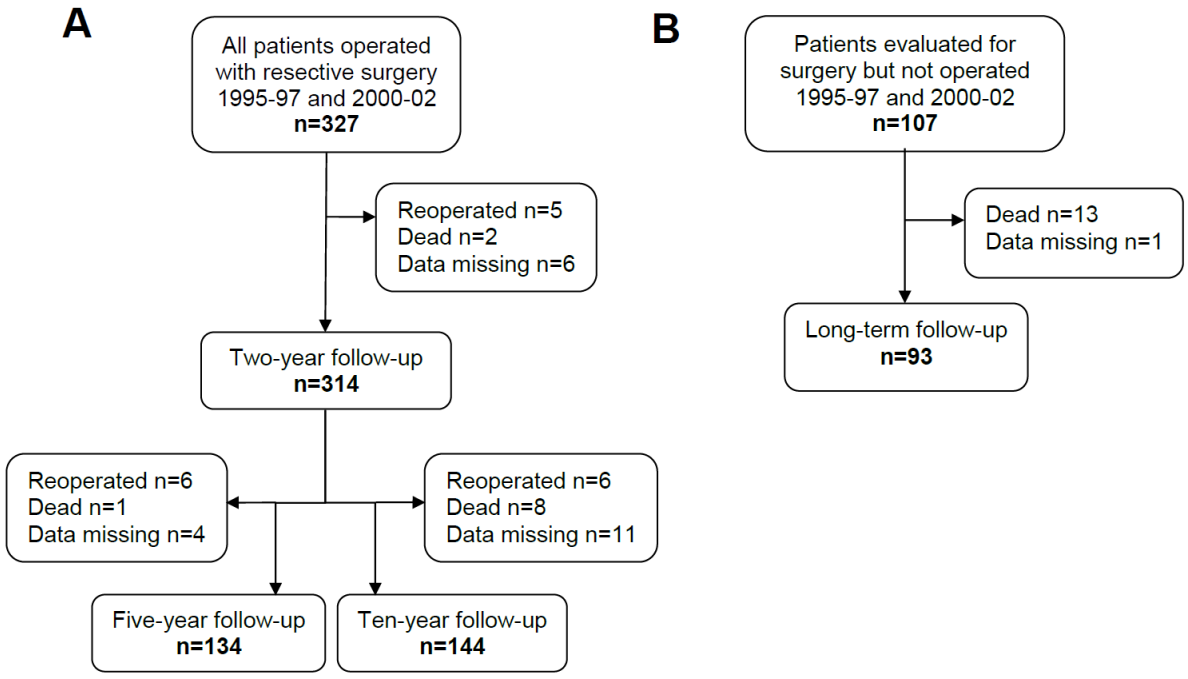


Figure 5. *Flowcharts for follow-up of patients (A) and controls (B) in Study I. A: Patients not followed up at two years: five children reoperated, two adults dead in epilepsy related death and one child and five adults lost to follow-up. Patients not followed up at five years: one child and five adults reoperated, one child dead (non-epilepsy related), one child and three adults lost to follow-up. Patients not followed up at ten years: one child and five adults reoperated, three children and three adults dead in epilepsy related death and one child and one adult in non-epilepsy related death, five children and six adults lost to follow-up B: All patients not followed up were adults, four deaths were epilepsy-related.*

Employment after resective surgery in adults was assessed in *Study II*. For this study, SNESUR data were analysed for all patients older than 18 years of age who had surgery 1995-2010. As shown in Figure 4, all patient cohorts in the study had two-year follow-up. Those operated 1995-2007 had at least one more follow-up, five or ten year, depending on which year the patient had surgery. Patients operated 1995-1997 also had 15-year follow-up. Re-operated patients had follow-ups after the most recent surgery, see Figure 6.

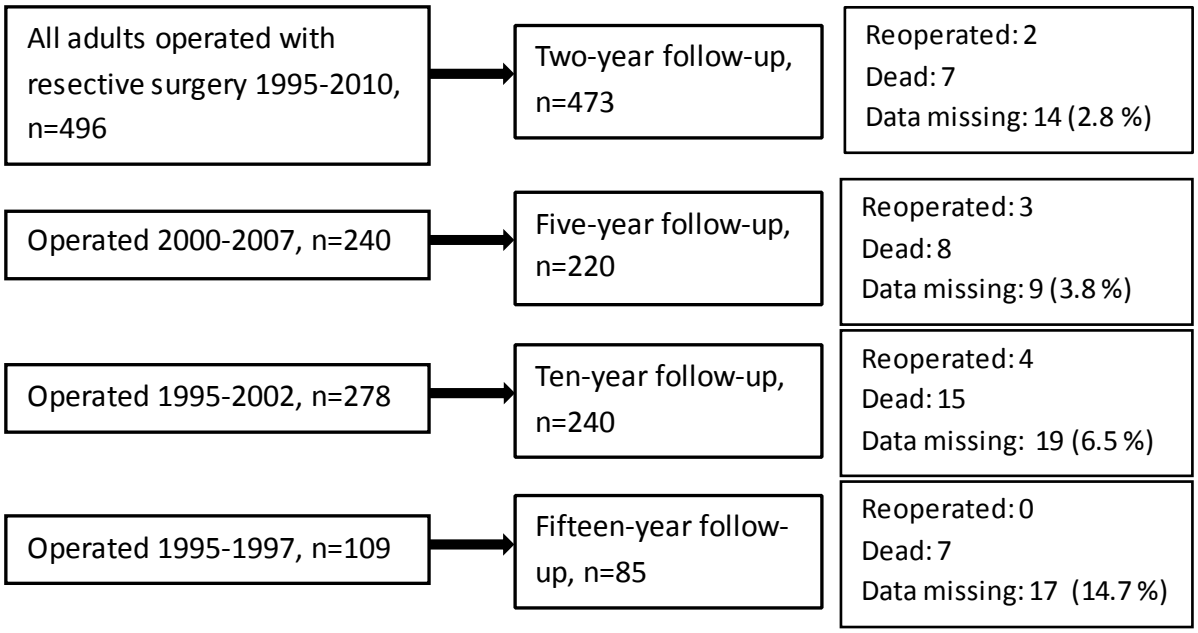


Figure 6. *Study II. Flowcharts for the four cohorts with follow-up after 2, 5, 10 and 15 years. Re-operated patients have follow-up from the last operation. 'Data missing' includes patients who could not be reached and those who declined participation.*

In Study II there was no control group of non-operated epilepsy patients. Instead, comparisons of employment status were made between seizure-free patients and the general Swedish population for the years 2005 to 2010. Data were obtained from Statistics Sweden (Statistiska Centralbyrån) from the Labour Force Surveys (Arbetskraftsundersökningarna) and stratified into age groups of decades from 25 years of age up to 64. Patients were stratified into the same age categories and compared with the general population.

Study III had a different design and was not based on data from SNESUR. This was a prospective population-based survey study including epilepsy surgery candidates (≥16 years) at all six Swedish epilepsy surgery centres 1995-1998. Patients were asked to complete questionnaires on health-related quality of life (HRQOL), depression, anxiety and additional questions at baseline and two years after epilepsy surgery or after pre-surgical investigations. Results from the two-year follow-up have been published.[142] For Study III, a cross-sectional long-term follow-up of this patient cohort was performed using the same questionnaires after 9-17 years (mean 14.5), see Figure 7.

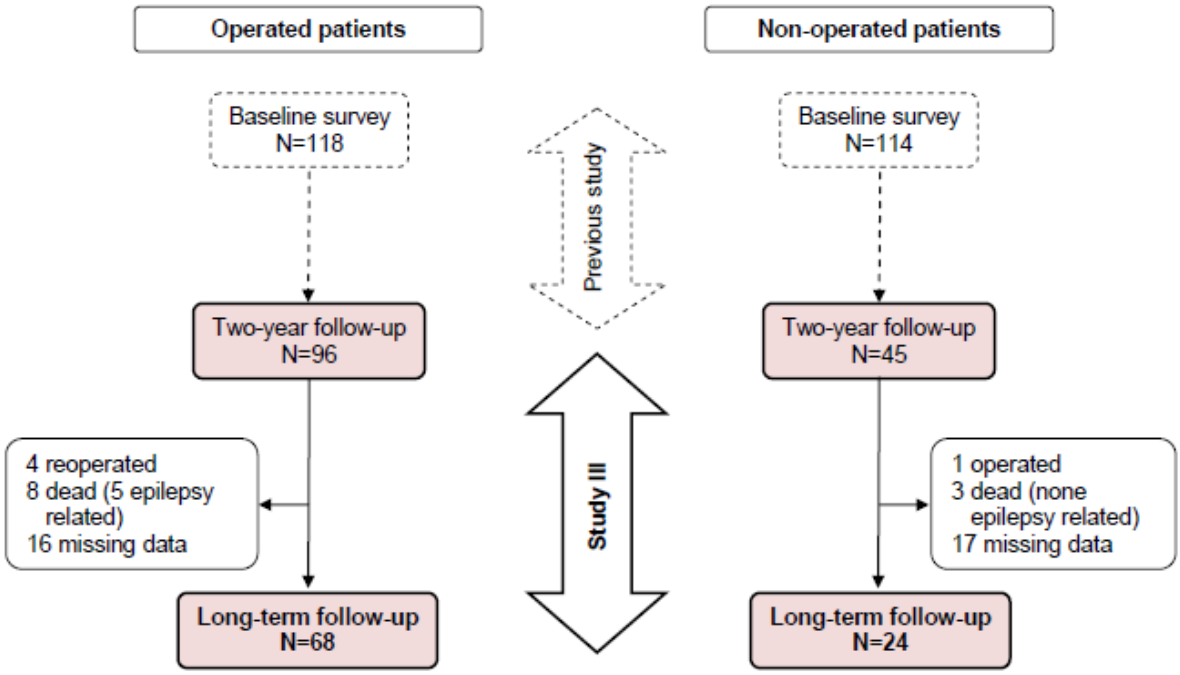


Figure 7. *Flowchart of patients and controls in Study III.*

7.2 Outcome measures

Seizure outcome

In Study I and II seizure outcome was classified according to seizure status during the last year before follow-up into the following categories:
a) seizure freedom with or without aura (ILAE Classes 1 and 2)
b) ≥75% reduction in seizure frequency compared to baseline
c) 50-74% reduction in seizure frequency
d) <50% reduction in seizure frequency
e) increased seizure frequency (only specified in Study I).
Patients who had been seizure-free since surgery (with or without aura, Engel I A+B[47]) were reported separately in Study I. In Study III seizure outcome was classified into seizure-free (ILAE Class 1 and 2) or not seizure-free. The limited number of patients precluded a more detailed classification of those not seizure-free.

Antiepileptic drug treatment

The number of AEDs at baseline and follow-ups was analysed for seizure-free adults and children in Study I.

Vocational outcome

Employment outcome (Study II) was categorized into full-time work (FW), part-time work (PW), full- or part-time studies (S), entirely on benefits (B, encompassing sick leave, disability pension and unemployment), or retired (R, i.e. old-age pension). Having employment was overriding, e.g. if a person was part-time working and part-time studying this would be classified as part-time work.

HRQOL outcome and emotional well-being

In Study III the 36-item Short Form Health Survey (SF-36) was used for assessment of HRQOL. The SF-36 is a generic instrument composed of eight domains: Physical Functioning (PF), Role Limitation-Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role Limitation-Emotional (RE) and Mental Health (MH). Domain scores range from 0 to 100, where higher scores correspond to better health. The domain scores may be summarized in two composite scores for physical health (PCS, physical component summary) and mental health (MCS, mental component summary), with a population mean of 50 and a standard deviation (SD) of 10. Changes in PCS and MCS scores were assessed using minimum clinically important difference (MCID) estimates that previously have been established for PCS (MCID=3.0) and MCS (MCID=4.6) in epilepsy patients.[61] For reference purpose, an age- and sex-matched sample (n=1196) was drawn from the Swedish SF-36 normative database, which contains data from 8,930 persons. Anxiety and depression were assessed using the Hospital Anxiety and Depression scale (HAD). This instrument contains 14 items, seven of which assess anxiety (HAD-A) and seven depression (HAD-D). Items are rated on a four-point Likert scale (0-3), with sums ranging from 0 (no symptoms) to 21 (maximal symptoms) for both anxiety and depression. Established cut-offs for non-cases (0-7 points), possible cases (8-10 points) and probable cases (11-21 points) were used for interpretation of scores.[145] Patient satisfaction with surgery was

addressed with separate questions, and patients were also asked if surgery had been harmful in any way.

Predictors of outcomes (Study I and II)

In Study I, prediction of seizure freedom was analysed for both operated patients and controls. Investigated variables were epilepsy duration in percent of life length (in order to compensate for the effect of age), ≥30 seizures per month and presence of secondary generalized tonic-clonic seizures (SGTCS). For the operated patients, additional variables were positive MRI (i.e. visible structural abnormality), resection types, and histopathology.

Predictive analyses for being employed vs not being employed were performed in Study II. Retired patients were excluded from analysis. The following variables were investigated: seizure outcome, preoperative vocational status, preoperative level of education, age (per decade of life), epilepsy duration in percent of life length, any neurologic dysfunction (including intellectual disability with a Full Scale IQ <70), sex, presence of SGTCS, and mean preoperative seizure frequency of ≥30 seizures per month.

7.3 Statistical methods

Study I and II: Descriptive baseline data were presented with means, standard deviations, medians and range. For comparison between two groups, Fisher's exact test was used for dichotomous variables, Mann-Whitney U test for continuous variables and Mantel-Haenszel Chi2 test for ordered categorical variables. All tests were two-tailed and conducted at the 5% significance level.

Univariate binary logistic regression analysis was performed for each independent variable to predict seizure freedom (Study I) or being employed (full-time or part-time, Study II). For analysis of employment, retired patients were excluded. Results were presented as odds ratios (OR) with 95% confidence intervals (95% CI). Independent variables attaining a significance level of $p<0.10$ were included in a forward stepwise multiple logistic regression analysis. For goodness of fit, the area under the receiver

operating characteristic curve (AUC) was calculated (Study I). Analyses were performed using IBM SPSS Statistics 19 and SAS 9.2.

Study III: Baseline data were presented with means, standard deviations and range. Descriptive analyses with comparison between two groups were performed with Fisher's exact test for dichotomous variables and Student's t-test for continuous variables. Non-parametric methods were used for analysis of SF-36 and HAD scores because of the non-normal distribution and the ordinal level of data. Between-group differences at specified time points were first analysed using Kruskal-Wallis test in comparison of three groups and then Mann-Whitney U test for pairwise comparisons. Within-group changes over time were analysed using Friedman test followed by Wilcoxon signed-rank test. Comparisons with the reference norm population were performed using Mann-Whitney U test. The Mantel-Haenszel Chi2 test was used for analysis of proportions of patients who reached MCID levels for SF-36, and proportions of non-cases, possible and probable cases with anxiety and depression (HAD scale), as well as for comorbidities and patient satisfaction. All tests were two-tailed and conducted at the 5% significance level. Standardized response means (SRMs) were used to estimate the magnitude of change between short-term and long-term follow-up for HAD scores, SF-36 domain and component summary scores (PCS and MCS). SRMs were calculated as the difference between the mean values, divided by the standard deviation of change scores. Scores were then interpreted using cut-offs suggested by Cohen: 0 to <0.2 as trivial, 0.2 to 0.5 as small, 0.5 to 0.8 as moderate and >0.8 as large.[146] Analyses were performed using IBM SPSS Statistics 22.

8 Results

8.1 Study I

Results for adults (n=190) and children (≤18 years, n=88) were reported separately and compared to controls. No significant difference was found in seizure outcome between the groups with five-year and ten-year follow-ups and these groups were merged into "long-term" in order to make comparisons with the control groups. Overall, 62% of the adults were seizure-free at long-term, compared to 14% of the controls ($p<0.001$). For the children, 50% were seizure-free at long-term, compared to 38% of the controls (not significant). Forty-one percent of adults had sustained seizure freedom since surgery at long-term versus 44% of the children, see Figure 8. Of those who were seizure-free at two-year follow-up, 87% were seizure-free also at long-term.

The most common resection type was TLR (154 adults and 38 children), where seizure freedom rates were 63% (adults) and 60% (children) at long-term. FLR was the second most common resection type (23 adults, 11 children), with 44% seizure-free adults and 27% seizure-free children. Seizure outcome differed depending on histopathology. Patients with cavernomas and neurodevelopmental tumours had the highest seizure freedom rates (78%), followed by hippocampal sclerosis (60%). Those with malformations of cortical development had the lowest rates, with 45% seizure-free.

Predictors for seizure freedom were examined both in operated patients and controls. In the multivariate analysis high seizure frequency at baseline (OR=0.40) and longer epilepsy duration (OR=0.91) were negative predictors and positive MRI (OR=1.96) a positive predictor of seizure-free outcome at long-term. No examined variables reached statistical significance in the controls.

An increasing proportion of seizure-free patients had discontinued AEDs at each follow-up, and after 10 years, 43% of the adults and 86% of the children had stopped medication ($p=0.002$). All of the seizure-free controls were still on AEDs.

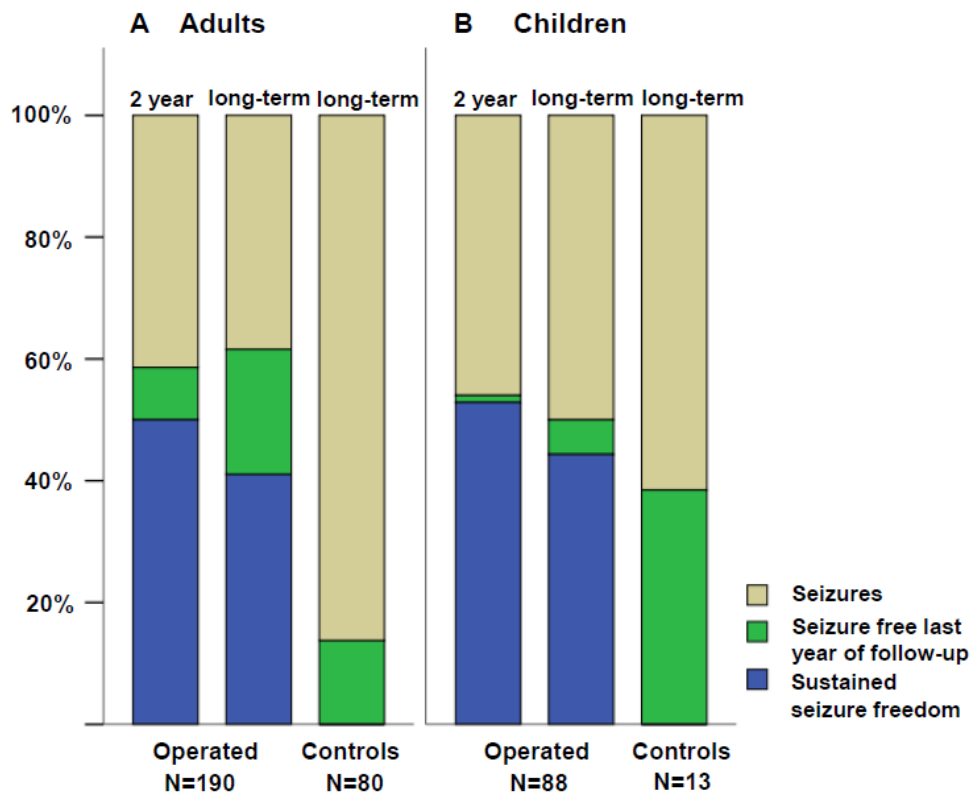


Figure 8. *Two-year and long-term follow-up (mean 7.6 years) seizure outcome for patients after resective epilepsy surgery compared to long-term follow-up (mean 9.2 years) of non-operated controls. Seizure-free patients include those with sustained seizure freedom with or without aura since surgery (blue) and patients seizure-free at least the last year before follow-up (green).*

8.2 Study II

Proportions of patients in full-time work (FW), part-time work (PW), students (S), persons on benefits (B) and retired (R) were largely unchanged from baseline through 2, 5, 10 and 15 years after surgery, except that S decreased and R increased. When grouped into four categories, as determined by baseline employment status (FW, PW, S or B) and when seizure outcome was accounted for, different patterns emerged. Patients in the FW group had the best employment outcomes after surgery, but even in the seizure-free group, the proportion of individuals in full-time work declined over time to 79%, 79%, 57% and 47%, respectively at the subsequent follow-ups. For the PW group employment outcome was mixed. Many patients with continuing seizures continued to work part-time long

after surgery. In the S group, those who became seizure-free later had full-time work in proportions similar to the FW group. In the B group, around 30% of seizure-free patients later had full-time employment. Most of those who did not become seizure-free continued on benefits.

Employment was compared to that of the general population, presented in four age groups of decades from age 25 to 64 in Figure 9. In the general population, 65-71% worked full-time between ages 25 to 54, but in the last age span (ages 55-64), only 53% worked full-time. This can be compared to seizure-free patients up to age 54 where 36-65% worked full-time after five and ten years. In the age span 55-64, only 24-27% worked full-time.

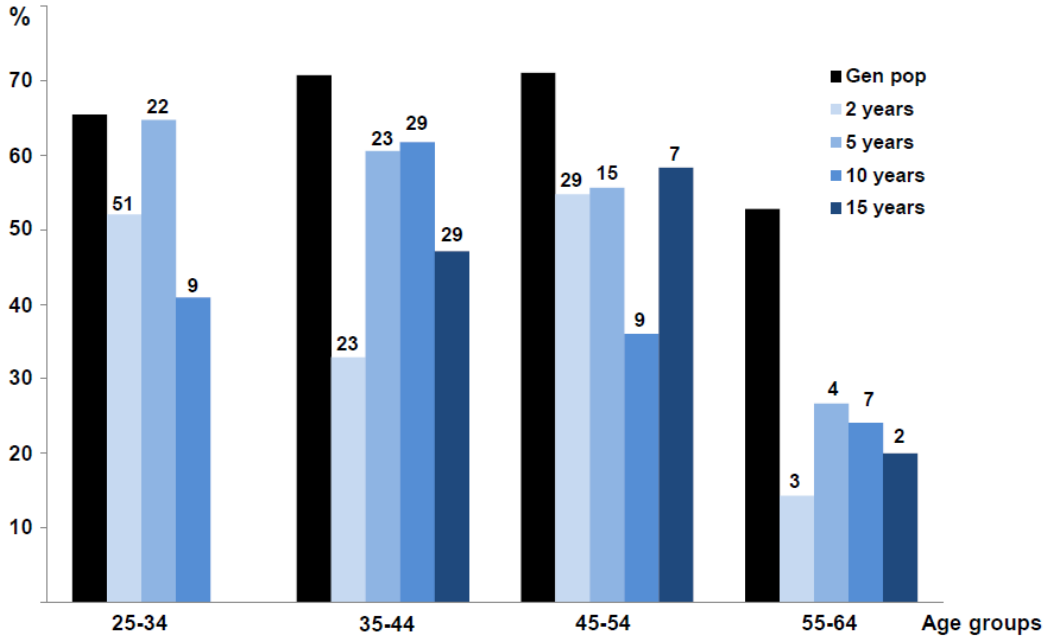


Figure 9. *Full-time employment for seizure-free patients and in the general population. Percentage with full-time employment in the general Swedish population (black bars) between 2005 and 2010, and in seizure-free patients (blue bars) at follow-ups 2, 5, 10 and 15 years after surgery. Data is shown for different age groups (decades). Numbers above bars represent no. of patients in each group. Gen pop = general population.*

Patients with university education had better vocational outcomes than those with compulsory school only. For seizure-free patients, ability to drive and having a family were associated with favourable employment outcome. The number of AEDs for seizure-free patients was analysed for employed versus not employed. There were significant differences, with fewer AEDs in the employed at two and five years, but with longer follow-up times this difference was no longer seen.

Predictors for employment were investigated. Variables significant in univariate analysis varied at different time points, but included seizure freedom, shorter duration of epilepsy, fewer seizures at baseline, male sex, younger age at surgery (in increments of 10 years), having employment pre-operatively and higher education. In the multivariate analysis pre-operative employment was the strongest predictor up to 10 years (at five years OR=13.7, at 10 years OR=6.5), followed by seizure freedom (OR=2.3 and 2.5, respectively) and younger age (OR=0.4 and 0.6, respectively). Fifteen years after surgery only seizure freedom remained predictive of employment (OR=10.3).

8.3 Study III

Seizure outcome at long-term was better for operated patients (Op; 75% seizure-free) than for controls (NO; 33% seizure-free; $p<0.001$). Seizure outcome was not static; 40/47 patients who were seizure-free at short-term were still seizure-free at long-term, and seven had relapsed. On the other hand, 10/21 patients who were not seizure-free at short-term were still having seizures at long-term, whereas 11 had become seizure-free. Among controls 3/24 were seizure free at short-term and eight at long-term.

SF-36 domain and component summary scores for operated patients and controls were compared to an age- and sex-matched population reference sample. Operated patients had the same or higher scores on all domains except Social Functioning and Mental Health. Physical Component Summary (PCS) was significantly higher than norm ($p=0.007$) and Mental Component Summary (MCS) lower than norm ($p=0.008$). Controls scored significantly worse than norm on five of eight domains as well as on both PCS ($p=0.041$) and MCS ($p=0.019$), see Figure 10.

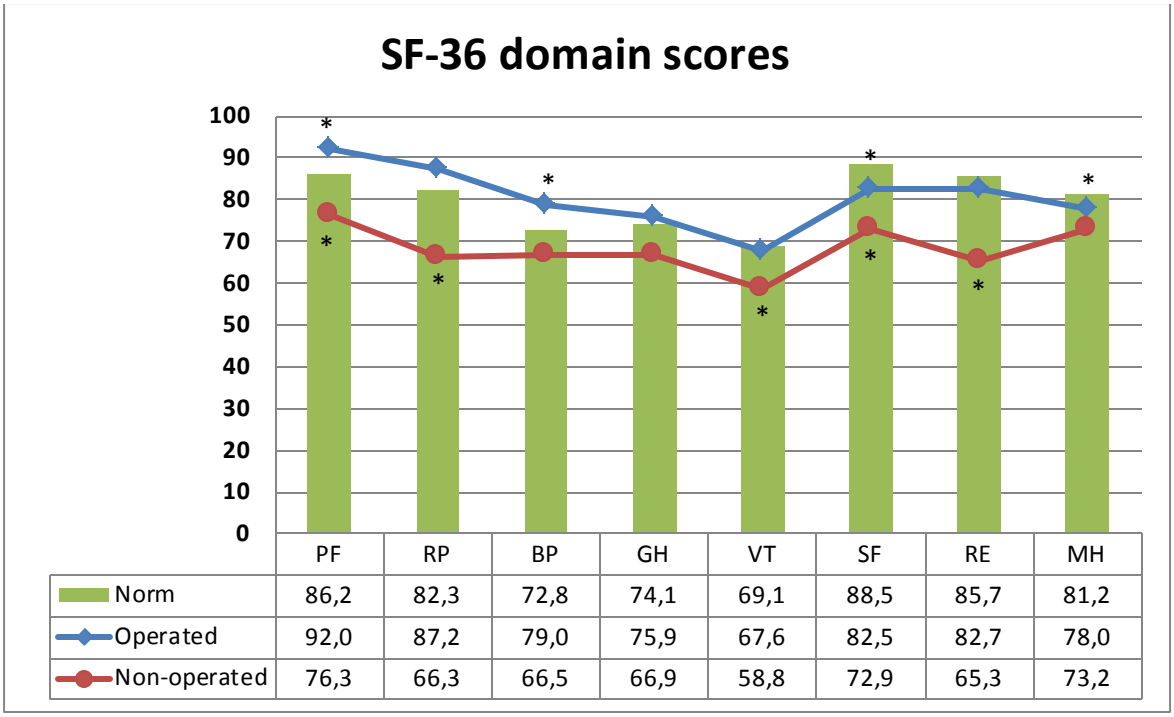


Figure 10. *SF-36 domain scores for operated patients and controls at long-term follow-up, compared to an age- and sex-matched norm reference (n=1196). Asterisks (*) mark where there were significant (p<0.05) differences to the norm population. Domains are PF=Physical Functioning, RP=Role Limitation-Physical, BP=Bodily Pain, GH=General Health, VT=Vitality, SF=Social Functioning, RE=Role Limitation-Emotional and MH=Mental Health.*

Mean group PCS and MCS values were calculated for controls and for operated patients at different time points. Operated patients who were seizure-free at short-term (OpF) showed significant improvement in both PCS and MCS scores from baseline to short-term and from baseline to long-term. Change in seizure status after short-term did not have an impact on mean PCS and MCS scores at long-term. Operated patients with persistent seizures at short-term (OpS) and controls did not have significant mean score changes over time.

The proportions of operated (Op) and controls (NO) reaching minimum clinically important difference (MCID) in change of PCS and MCS were investigated. Improvements from baseline to long-term in PCS were seen in 50% of Op and 33% of NO, and deterioration in 18% of Op and 38% of NO. For MCS, improvement was seen for 47% of Op and 38% of NO, worsening in 22% of Op and 38% of NO (non-significant). No differences were seen between operated and controls from short-term to long-term.

Comorbidity had no impact on PCS or MCS in operated patients, but controls with comorbidities had worsening and those without comorbidities had improvements in PCS ($p=0.070$) and MCS ($p=0.029$).

Few patients had possible or probable depression or anxiety. At short-term, more controls than operated seizure-free had possible or probable anxiety or depression. No significant group differences were seen at long-term.

Nearly all operated patients considered surgery overall beneficial (98% of seizure-free and 88% of not seizure-free). More of those seizure-free were satisfied with surgery (88%) than of those not seizure-free (63%, $p=0.006$). Fifteen percent thought that surgery had caused some harm; memory problems and visual impairment were the most common reasons given.

9 Discussion

The aims of this thesis were to investigate long-term outcomes after resective epilepsy surgery with regard to seizures, AEDs, employment and HRQOL. We found that around two thirds of TLR patients and about one third of those with extratemporal resections were seizure-free at long-term follow-up. AED reduction is time-dependent and more seizure-free children than adults stop medication. Seizure freedom is important for employment outcome in adults, but many other factors influence employment and few patients can work full-time up to retirement. HRQOL is better in operated patients than in controls. At group level HRQOL results are stable from two years postoperatively, but individual improvement or worsening of quality of life is common.

9.1 Seizure outcome

Studies based on the Swedish National Epilepsy Surgery Register fulfil several requirements for high quality studies, with population-based cohorts (thus avoiding selection bias), prospective collection of data and longitudinal follow-ups at defined time points. Our findings that 63% of adults and 60% of children were seizure-free (ILAE class 1 and 2) after TLR at the long-term follow-up parallel those of other prospective longitudinal studies.[26, 63, 69, 147] As expected, seizure freedom rates were lower after FLR and other extratemporal resections, similar to the results of earlier studies.[70, 82]

There are only a few long-term reports from population-based cohorts. In a cross-sectional study from Ireland, long-term seizure outcome was reported in a national survey. Ten years after resective surgery, 44% of patients who answered the survey were seizure-free (Engel class I), but the total number of operated patients was unknown.[148] A retrospective Norwegian survey study in children (where the response rate was 70%) reported that 58% were seizure-free (Engel class I) after a mean of seven years.[72] Our study was prospective, with a small number of drop-outs.

Long-term outcome studies of epilepsy surgery share the problem of identifying representative controls. Control groups usually consist of epilepsy surgery candidates who for some reason never were operated. This imposes a bias on these studies, but it is difficult to see how a more representative control group could be identified. It is likely that patients undergoing epilepsy surgery evaluation are in a more severe state, or at the 'nadir' of the disease course, and that regression to the mean will account for some of the improvement seen over time.[149] Bearing this in mind, controlled studies are still an important part of epilepsy surgery outcome research. A systematic review of studies comparing surgical results to those of a non-surgical control group identified 13 studies with a follow-up of at least four years.[150] Overall 44% of surgical patients were seizure-free at follow-up compared to 12% of medically treated patients, which is comparable to our study with 58% seizure-free last year of follow-up in the surgical group and 17% in the non-surgical group, children and adults being grouped together.

The chance of being seizure-free at long-term follow-up in our study was 87% for those who were seizure-free at the two-year follow-up. Similar results were seen in the UCL study, where seizure freedom at two years predicted an 86% chance of seizure freedom at five years, and 78% at 10 years.[63] This information is highly relevant for the individual patient.

In the multivariate analysis we found high baseline seizure frequency and epilepsy duration to be negative predictors, and findings on MRI to be a positive predictor for long-term seizure freedom. The duration of epilepsy in adults referred for pre-surgical evaluation is still 15-20 years.[151] Studies comparing surgery over different time periods show that epilepsy duration before surgery has not changed over the years.[25, 62, 87, 152] Earlier epilepsy surgery has the important potential to decrease or even prevent some of the disabling psychological and social consequences of long-standing epilepsy. Under-referral of epilepsy surgery candidates is generally considered to be a problem and this has been investigated in one Swedish study where potential candidates for epilepsy surgery were identified using pre-specified criteria. This study identified 28 of 48 potential candidates as inappropriately not referred for pre-surgical evaluation, corresponding to an estimated number of 60 'missed referrals' per 100,000 inhabitants.[153]

9.2 Antiepileptic drug treatment

Opinions on AED management after successful surgery differ and there is no consensus on strategy for withdrawal of medication. In Sweden, most adults continue AED treatment the first two postoperative years. After that decisions about withdrawal are individualized. For children AED tapering is usually attempted earlier. In our study, twice as many seizure-free children as adults had ceased AED medication at long-term, and the proportions without AEDs were increasing with longer follow-up times. Several previous studies have found similar results, with more children than adults having discontinued AEDs.[107, 154] Adults have other aspects to consider when deciding for or against AED discontinuation, not least the psychosocial consequences of seizure recurrence with regard to occupational ability or driving. For some patients, reduction to monotherapy in a low dose may be optimal and in our study, the proportion of seizure-free adults who had no or one AED increased to almost 80% after 10 years. For children, adverse cognitive effects of AEDs may hamper development and AED reduction is often attempted at an earlier stage than in adults.[155] AED outcome is highly time-sensitive. It is therefore difficult to draw conclusions from cross-sectional data and AED outcome should be recorded longitudinally. Two long-term studies with follow-up 12 years after surgery in adults reported that 29% and 48% of those seizure-free had ceased AED treatment.[110, 156] A similar long-term study, also with 12 year follow-up, reported AED discontinuation in 82% of seizure-free children.[73]

The proportion of seizure-free patients without AEDs after surgery is dependent on follow-up time, but also on attitudes and opinions among caregivers and patients. In one Indian study reporting on outcome after early tapering of medication, the authors point out that the cost of medication, the availability of public transport and the family support around persons with epilepsy are reasons for early AED reduction in their cohorts.[93] These are factors that are likely to vary across studies from different countries.

In patients with seizure relapse during or after tapering of AEDs, the development of therapy resistant epilepsy after reinstitution of AEDs appears to be around 30%, but causality is difficult to analyse.[154, 155, 157] For

the individual patient, it is not possible to know if the relapse was a consequence of AED tapering or if it would have occurred anyway. From the currently available evidence, it seems that AED withdrawal discloses surgical accomplishment, without influencing long-term seizure outcome.[101,155] The timing and decision to withdraw must be individualized and is ultimately the patient's choice. Furthermore, some patients may choose to remain on a tolerable dose of one AED.

9.3 Vocational outcome

In Study II, no net employment gains were found in the whole cohort of operated patients. More detailed analysis showed different patterns depending on pre-surgical vocational status and seizure outcome, with the best results for those with full-time employment before surgery and seizure-free outcome. However, the proportion who worked full-time decreased over time. This implies that not only seizure freedom is important for working ability. Students had similar employment outcomes to those with preoperative employment, which is similar to results from other studies.[118, 122] The least favourable results were seen in those on benefits before surgery, but after five and 10 years around 30% of those who became seizure-free in this group worked full-time. This can be compared to results from the US Multicenter study, where 25% of those disabled or unemployed before surgery worked at least part-time after two years.[116]

In the multivariate analysis two, five and 10 years after surgery, pre-operative employment was the strongest predictor for employment, followed by seizure freedom and younger age at surgery. This is in contrast to the majority of other studies, where seizure freedom has been the strongest predictor for employment after surgery.[51] However, after 15 years, seizure freedom was the only remaining predictor for employment.

Comparison of studies from different countries and time periods may be difficult. Different socioeconomic and political structures as well as changing employment opportunities over time epochs can play important roles for vocational outcomes. In our study, this is compensated for by the comparison to the general population and by the longitudinal study design. The observed decrease in full-time employment during the last decade of

working life was seen also in the general population, but to a lesser degree. Interestingly, the same pattern has been reported in other studies of persons with neurologic dysfunctions. One prospective Swedish study of young adults with cerebral palsy or spina bifida found decreasing full-time employment rates over a period of 14 years.[158] One explanation for this could be that the ageing process affects people with disabilities earlier in life. Education, social support from family and friends, cognitive function, ability to drive and mental health are other factors that influence employment. The number of AEDs in seizure-free patients was lower for those employed at two and five years, but not at later follow-ups. Fewer AEDs may imply fewer side-effects which in turn might improve working capacity.[159]

Some issues that may influence the reporting of employment outcome should be considered. Adapted, subsidized work is sometimes available for people with disabilities of varying degree and in evaluating employment outcome this is seldom reported separately. Furthermore, the distinction between unemployment and inability to work because of illness or disability is not always clear. This issue also involves the prevailing social security systems, which differ from one country to another, but also change over time. A patient who is unemployed in one country might receive disability pension in another. In order to deal with this problem in our analyses, people with unemployment and those who were on sick leave or receiving disability pensions were grouped together.

Patients with higher education had better vocational outcomes than those with only compulsory school. In the seizure-free group, driving and having a family were associated with better employment outcome. All these factors can be viewed as markers of a generally higher social functioning capacity rather than predictors for employment.

The value of structured vocational rehabilitation has been studied in epilepsy surgery patients and compared to a historical control group in one study. Participation in the rehabilitation program had the same effect on employment outcome as seizure freedom, which should be considered post-surgery.[127]

9.4 Health-related quality of life

Study III was a follow-up study 14 years after epilepsy surgery or pre-surgical evaluation. A two-year follow-up study of this cohort found improvements in all SF-36 domains for those operated and seizure-free, and no changes for the operated patients with persistent seizures or for the control group.[142] At long-term, the only statistically significant change in SF-36 domain scores was a small positive change in Physical Role-Limitation for operated patients who had seizures at short-term, indicating stable results at group level. Previous studies with shorter follow-ups, where results are presented with mean scores or mean change of scores, have reported stability of HRQOL scores at group level after an initial positive change occurring within six months to three years after surgery.[24, 25, 132, 138, 139, 156, 160] Changes in seizure status from short-term to long-term follow-up complicate long-term analysis and interpretation. Mean PCS and MCS values in groups with different seizure outcome showed very little change from short-term to long-term, suggesting that factors other than seizure freedom may be more important for HRQOL at long-term. However, analysis using MCID showed that a considerable proportion of patients and controls had either improvement or deterioration of HRQOL. This provides information on HRQOL change at an individual level and is an important complement to mean value analyses. No other long-term study of HRQOL after surgery has explored changes using MCID.

In our study, operated patients reached the same or higher SF-36 scores as a matched norm population in all domains except Social Functioning and Mental Health. Similar results were found for seizure-free patients in the US Multicenter study five years post-surgery,[132] and in some studies with shorter follow-ups comparing results to those of a medical control group.[136, 156, 161] It is possible that cognitive (e.g. memory impairment or mental fatigue) or emotional problems (depression or anxiety) have a negative influence on social function.[133, 134, 162] Employment has also been shown to be closely related to better HRQOL, but relationships between seizure and employment outcomes are complex and seizure freedom after surgery does not automatically lead to improvements in employment, as shown in Study II.[116, 137, 147]

One factor that needs some consideration in interpreting changes in HRQOL after any intervention is the phenomenon of reprioritization of what's important in life. This has been investigated in several studies using a variety of methods, where patients have rated the relative importance of HRQOL domains at various time points, e.g. before and after various treatments.[163] There is only one study on the reprioritization response shift after epilepsy surgery.[164] Here, it was shown that the mean scores of all QOLIE-31 domains, except overall quality of life, were higher in the surgical group than in the control group one year after surgery. When the relative importance of the domains was assessed before and after surgery, the importance of seizure worry decreased and the importance of social functioning increased. One interpretation of this response shift may be that postoperative seizure freedom makes it possible to take part in social activities in a way that was not possible before surgery, and social difficulties that patients encounter now become evident. Therapy resistant epilepsy through childhood and adolescence might contribute to dysfunctions that are very difficult to normalize later in life. It is possible that long-standing problems in social functioning may not be completely reversible.[165]

Several authors have emphasized the importance of exploring individual trajectories for psychosocial outcomes and HRQOL after epilepsy surgery.[166,167] However, exploration of HRQOL patterns in our cohort failed to identify specific patterns. It is likely that many factors affect a person's HRQOL, complicating the analysis. As for seizure outcome, regression towards the mean is likely to account for some of the improvement seen in HRQOL outcome long after surgery.[149, 166]

Mood has a very strong impact on quality of life and previous studies have found lower HRQOL levels in patients with depression or anxiety.[134, 168] However, in our study few patients had possible or probable anxiety or depression, and none of the observed differences between operated seizure-free, not seizure-free or controls were significant. The percentages with possible or probable anxiety were higher than those with depressive symptoms, similar to results from other studies.[169, 170]

Patient satisfaction with surgery is another important topic. Eighty-two percent of patients were very satisfied or satisfied with surgery, seizure-free patients to a higher degree than those not seizure-free. No patient was

dissatisfied or very dissatisfied. A review published in 2011 identified eight studies reporting on patient satisfaction with epilepsy surgery.[171] Follow-up times ranged from 2 months to 20 years. A pooled data analysis found patient satisfaction with epilepsy surgery to be 71%. Only three patients (4%) in our study regarded surgery to have been not overall beneficial. One was seizure-free without adverse effects, the other two had fewer seizures than before surgery and one of them had adverse effects of surgery (memory and visual impairment). Satisfaction and dissatisfaction are multifaceted constructs which require more in-depth analysis for interpretation.[172]

HRQOL instruments can be considered as the looking glasses through which we think we can assess how patients experience their lives, but this may not necessarily be a true reflection. Results could be regarded as indicators of quality of life rather than representing HRQOL per se. Qualitative studies are remarkably scarce, but constitute an important complement to get a more thorough understanding of patients' views and to identify areas where caregivers should provide better support.[104] Although epilepsy affects many aspects of life and stigmatization is still present, many other factors unrelated to epilepsy are important and will influence quality of life.

9.5 Strengths and weaknesses

The main strength of the three studies is the prospective, longitudinal and population-based design. Study I and II are based on data from SNESUR. The national coverage of SNESUR is dependent on a collaborative network, where all six surgical centres report patient data using structured protocols at pre-defined time points. To date, SNESUR contains follow-up data up to 20 years after surgery, with few missing follow-ups. Comparison to control groups in Study I and III are further strengths of these studies. Study II has no control group, but it is the only employment outcome study after epilepsy surgery where comparison has been made with the general population. This provides valuable information and gives a perspective which compensates for changes in society. In Study III HRQOL scores are compared to controls as well as to a matched norm sample. The use of MCID cut-offs for appraisal of meaningful change is another strength of Study III.

Weaknesses in Study I include that the controls do not constitute a national sample, and that the group of children is small. In SNESUR, yearly follow-ups on a national level have not been possible, precluding the possibility to make survival analyses of seizure freedom. Register based studies have limitations on the number of variables that can be assessed and further analysis of possible associated factors is not always feasible. Comorbidities and completeness of resections are examples of such factors that could not be accounted for. The development of neuroimaging techniques and changes in histopathological classifications over the years also complicate analyses of these variables. In Study II, the extent of part-time work and occupational categories could not be addressed for estimation of underemployment. In Study III the small sample size and the number of missing patients is a problem, especially considering that patients missing at long-term had higher anxiety and depression scores at short-term follow-up, than those who participated in the long-term study. Furthermore, the proportions of missing patients and controls differ. Study III was planned before QOLIE-89 was available. The use of an epilepsy specific HRQOL scale might have enhanced sensitivity of changes in HRQOL after surgery. Another drawback is the cross-sectional follow-up. However, it seems plausible that the long duration of follow-up could compensate for this.

10 Conclusions

In these studies seizure freedom last year of follow-up was achieved by around 60% of patients after TLR and by 30-40% after other types of resections. Seizure outcome was partly dependent on histopathological diagnosis, with better results for patients with localized lesions than for those with more diffuse or wide-spread pathology. In the multivariate analysis MRI findings, lower seizure frequency at baseline and shorter epilepsy duration were predictive of seizure freedom. The vast majority of seizure-free children and almost half of seizure-free adults had stopped AED medication after 10 years.

Vocational outcome is an important outcome measure for several reasons. Patients with preoperative employment and postoperative seizure freedom were shown to have the best employment outcomes. In addition, younger age at surgery was predictive of postoperative employment. However, a declining proportion continued to work full-time, especially towards the end of the expected working period in life. Patients with benefits before surgery were employed to a lesser extent after surgery, although almost a third of those who achieved seizure freedom were employed full-time at long-term.

Epilepsy surgery often leads to an improvement in HRQOL, which in our and others' studies has been shown to stabilize two years after surgery. Seizure freedom does not automatically lead to better HRQOL, but it is the most consistently identified predictor. However, in our study a significant proportion of patients later improved or deteriorated in HRQOL independent of seizure outcome. Social functioning and mental health are domains where problems persist even long after surgery.

Shorter duration of epilepsy and younger age were predictive of seizure freedom and employment, pointing to the importance of early identification of epilepsy surgery candidates. It is likely that long-standing therapy resistant epilepsy has negative effects that are not completely reversible. Most patients are children and young adults, and in the pre-surgical counselling process individualized information on expected long-term outcomes is essential. Seizure freedom and improved employment and

quality of life can never be guaranteed, but longitudinal studies such as these can provide patients with estimations of expected outcomes, not only a few years after the operation. Having realistic expectations of what epilepsy surgery can change in life is likely to promote increased HRQOL and contribute to higher patient satisfaction with surgery.

11 Future perspectives

The majority of studies on epilepsy surgery outcomes have methodological shortcomings likely to affect the results, e.g. retrospective design, cross-sectional assessment, a single follow-up time point or lack of adequate controls. Meta-analyses and structured reviews based on studies of different design will incorporate the weaknesses of the original studies, making it difficult to draw conclusions. Furthermore, there is considerable variability between studies on vocational and other psychosocial outcomes and HRQOL. Future studies need to account for multiple factors that are likely to affect these outcomes. They should have control groups of non-surgical epilepsy patients, or other reference populations. Longitudinal follow-ups are crucial for the assessment of dynamic outcomes. Identification of individual trajectories is highly relevant for individual risk-benefit consideration. A lifespan perspective is necessary to better understand the impact of surgery at different ages. The value of a specific vocational rehabilitation program for employment outcome has been demonstrated in one study and needs to be further developed and investigated.

In order to further improve outcome, future studies should focus not only on success, but also on 'surgical failures', e.g. relapse of seizures, extent of complications, decrease in HRQOL and dissatisfaction with epilepsy surgery.[173] Qualitative investigations may add further perspectives on patients' expectations on and experiences of epilepsy surgery, which could provide new insights into how epilepsy surgery teams can help patients to have realistic expectations and to optimize their postoperative coping.

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14 Original publications