Surgical and neurological adverse effects of epilepsy surgery

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Gothenburg, Sweden, 2019

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ISBN 978-91-7833-646-3 (PRINT)
ISBN 978-91-7833-647-0 (PDF)
http://hdl.handle.net/2077/60789

Printed by BrandFactory, Gothenburg, Sweden 2019

Clinical cases are personal as much as they are scientific problems, and the clinician must often make the best compromise with perfection that he can. He must understand the patient and his hopes before he presumes to decide on treatment. But this is, after all, the secret of the art in the practice of medicine.

Wilder Penfield and Kenneth Paine,
Results of surgical therapy for focal epileptic seizures (1955)[1]

Abstract

The aim of this thesis was to study surgical and neurological complications of preoperative invasive investigations and epilepsy surgery procedures (Papers I-II) and seizure worsening after epilepsy surgery (Paper III). A further aim was to improve reporting of adverse effects related to invasive investigations and epilepsy surgery by proposing and evaluating an evidence-based protocol for monitoring complications (Paper IV).

Papers I-III were based on data from the prospective Swedish National Epilepsy Surgery Register. In Paper IV, a literature review of previous definitions and classifications of complications in epilepsy surgery was the starting point for a consensus-based proposal agreed within an international network of epilepsy surgery centers. The final protocol was clinically evaluated at three of the centers during a period of one year.

Complications were seen in 4.8% of 271 invasive EEG procedures, none of which were major. Subdural grids had the highest risk. Complications related to invasive investigations increased the risk for complications related to subsequent epilepsy surgery (Paper I). After 865 epilepsy surgery procedures, major complications were seen in 3.0%, and minor complications in 7.5%. Higher age at surgery was a risk factor for complications (Paper II). After 1407 epilepsy surgery procedures, increased seizure frequency occurred in 4.0% cases, and new-onset tonic-clonic seizures in 3.9%. Both outcomes were more common in reoperations. Lower age at surgery and extratemporal procedures were independent risk factors for increased seizure frequency, and preoperative neurologic deficits for new-onset tonic-clonic seizures (Paper III). The agreed protocol for complications was used for 90 procedures with a total of 18 complications (not differentiated into major or minor). Areas for future improvements of the protocol were identified (Paper IV).

Complications and seizure worsening are rare outcomes after epilepsy surgery. Robust data on negative outcomes are important in order for patients and parents to make informed decisions about epilepsy surgery. Prospective data collection with standardized protocols may improve reporting of adverse effects.

Sammanfattning

Epilepsikirurgi är en behandling för epilepsi som används för vissa patienter som inte blir anfallsfria med enbart läkemedel. Behandlingen innebär att ett område i hjärnan där epileptiska anfall uppkommer opereras bort eller avgränsas från övriga delar av hjärnan. De personer som kan opereras kan bli helt anfallsfria eller få en förbättrad anfallssituation och livskvalitet.

Som vid alla operationer finns det risker som patienterna och deras närstående behöver få information om och diskutera innan de tar ställning till operation. Det kan uppstå kirurgiska komplikationer som infektion eller blödning. Neurologiska funktioner kan försämras, ibland oväntat och i vissa fall förväntat på grund av att man har opererat i områden som är viktiga för speciella hjärnfunktioner. En liten andel av patienterna får fler eller allvarligare epileptiska anfall jämfört med före operationen.

Elektroencefalogram, EEG, används för att avläsa elektrisk aktivitet från hjärnan. Under utredningar för epilepsikirurgi behövs ibland tillfälligt inopererade EEG-elektroder för att kartlägga var patientens anfall uppkommer och avgöra vad man kan operera bort utan att skada viktiga hjärnfunktioner. Utredningen är i dessa fall nödvändig för att bedöma om epilepsikirurgi kan erbjudas men innebär i sig också en viss risk.

Denna avhandling bygger på fyra delstudier som berör kirurgiska och neurologiska komplikationer i samband med epilepsikirurgi och utredning med inopererade EEG-elektroder samt försämring av anfallssituationen efter kirurgi.

I den första studien använde vi det nationella kvalitetsregistret, Svenska epilepsikirurgiregistret, för att studera komplikationer efter utredning med inopererade EEG-elektroder.

Komplikationer uppkom i samband med 4,8 % av de 271 ingrepp av denna typ som gjordes i Sverige 1996–2010. Inga av komplikationerna ledde till bestående symtom eller dödsfall. Blödning var den vanligaste komplikationen. Risken för komplikationer var högst för utredning med elektrodplattor på hjärnytan, vilket stämmer med andra studier. Om patienten fick en komplikation av de inopererade EEG-elektroderna var risken högre att samma patient skulle få en komplikation efter senare epilepsikirurgi. Detta har inte beskrivits tidigare, och det behövs mer forskning för att ta reda på vad det beror på.

I den andra studien undersökte vi kirurgiska komplikationer och neurologisk försämring efter de 865 epilepsikirurgiska ingrepp som gjordes i Sverige under samma period, 1996–2010. Också detta arbete bygger på uppgifter från Svenska epilepsikirurgiregistret.

Efter 3,0 % av operationerna uppkom komplikationer som klassificerades som allvarliga, definierat som att de ledde till symtom som fanns kvar under minst tre månader. Mindre allvarliga komplikationer uppkom i 7,5 % av fallen. Inga dödsfall rapporterades. Infektion och blödning var de vanligaste kirurgiska komplikationerna, medan svaghet i ena armen eller benet var den vanligaste formen av neurologisk försämring. Resultaten stämmer väl överens med internationella studier som gjorts med liknande metoder.

I en analys av riskfaktorer fann vi att risken för komplikationer är något högre ju äldre patienten är vid operationen. Man kan behöva ta hänsyn till detta när man överväger kirurgi, men det utesluter inte att äldre personer kan opereras med goda resultat.

Den tredje studien handlar om försämring av anfallssituationen och bygger på data från Svenska epilepsikirurgiregistret om epileptiska anfall före och efter operation. Vi studerade utfallet efter de 1407 epilepsikirurgiska ingrepp som gjordes i Sverige 1990–2013. Vid uppföljning efter två år hade 4,0 % fler anfall per månad än de hade före operationen, medan 3,9 % hade nytillkomna tonisk-kloniska anfall, en mer allvarlig anfallsform. Eftersom det inte fanns någon kontrollgrupp i studien kan vi inte säkert avgöra om försämringen beror på operationen eller om den hade uppkommit ändå.

Man vet inte varför vissa personer blir försämrade efter epilepsikirurgi. Vi fann att risken var högre om patienten hade genomgått epilepsikirurgi tidigare. Risken för fler anfall var högre för yngre patienter och för operationer i andra delar av hjärnan än tinningloberna. Nytillkomna tonisk-kloniska anfall var vanligare bland personer med neurologisk funktionsnedsättning. Vi tror att förklaringen kan vara att dessa personer kan ha mer utbredda nätverk av nervceller där anfallen startar och sedan sprids.

Eftersom komplikationer är ovanliga behövs det stora studier för att undersöka riskfaktorer. Standardiserade protokoll ökar säkerheten i rapporteringen, och Svenska epilepsikirurgiregistret är gemensamt för alla sjukhus som utför epilepsikirurgi i Sverige. Sjukhus i andra länder har rapporterat komplikationer på många olika sätt, vilket gör att det är svårt att jämföra resultat mellan olika studier.

För att undersöka vissa typer av samband skulle det behövas internationella studier där alla deltagande sjukhus använder samma typ av rapportering. Den fjärde studien syftade till att arbeta fram ett vetenskapligt grundat protokoll för sådana studier.

Först gjorde vi en litteratursökning för att identifiera definitioner och klassifikationer som har använts tidigare. Baserat på denna genomgång tog vi fram ett förslag till ett protokoll, som bearbetades och till slut godkändes inom internationella samarbetsorgan för epilepsikirurgi. Protokollet utvärderades genom att tre av de deltagande sjukhusen, i Göteborg, Lyon och London, använde det för alla ingrepp som utfördes under loppet ett år.

Hittills har man rapporterat 18 komplikationer under 90 ingrepp. För fyra patienter kvarstod symtom vid sex månaders uppföljning. Rapporteringen fungerade i stort sett väl och vi kunde identifiera vissa delar av protokollet som man behöver arbeta vidare med.

Komplikationer och försämrad anfallssituation är ovanligt efter epilepsikirurgi. Uppgifter om möjliga negativa utfall behövs för att sjukvården ska kunna fatta välgrundade beslut om att erbjuda kirurgi. Det är också nödvändigt för information till patienter och närstående, där man samtidigt väger in den stora nyttan med epilepsikirurgi och riskerna med svårbehandlad epilepsi. För att analysera riskfaktorer behövs det större studier med flera deltagande sjukhus. Standardiserade protokoll kan förbättra rapporteringen i sådana studier. Det behövs också mer forskning för att utveckla säkrare utfallsmått för hur komplikationer påverkar dagliga aktiviteter och livskvalitet.

List of papers

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

I. Hedegärd E, **Bjellvi J**, Edelvik A, Flink R, Rydenhag B, Malmgren K.
Complications to invasive epilepsy surgery workup with subdural and depth electrodes: a prospective population-based observational study.
Journal of Neurology, Neurosurgery, and Psychiatry 2014; 85: 716-720.

II. **Bjellvi J**, Flink R, Rydenhag B, Malmgren K.
Complications of epilepsy surgery in Sweden 1996–2010: a prospective, population-based study.
Journal of Neurosurgery 2015; 122: 519-525.

III. **Bjellvi J**, Edelvik A, Rydenhag B, Malmgren K.
Risk factors for seizure worsening after epilepsy surgery in children and adults: a population-based register study.
Neurosurgery, in press.

IV. **Bjellvi J**, Cross JH, Rheims S, Ryvlin P, Sperling MR, Rydenhag B, Malmgren K.
Complications in epilepsy surgery and invasive diagnostic procedures: a proposed protocol and feasibility study.
Manuscript.

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Abbreviations

ADL	Activities of daily living
AED	Antiepileptic drug
ATL	Anterior temporal lobe resection
CI	Confidence interval
EEG	Electroencephalography
fMRI	Functional magnetic resonance imaging
ILAE	International League Against Epilepsy
LTM	Long-term video-EEG monitoring
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
NSQIP	National Surgical Quality Improvement Program
RCT	Randomized controlled trial
SAH	Selective amygdalohippocampectomy
SDE	Subdural exploration
SEEG	Stereo-electroencephalography
SNESUR	Swedish National Epilepsy Surgery Register
SUDEP	Sudden unexpected death in epilepsy
TCS	Tonic-clonic seizure
TLR	Temporal lobe resection
VFD	Visual field defect

Introduction

Epilepsy surgery aims to treat seizures in children and adults with drug-resistant epilepsy. Before consenting to this treatment option, the patient and, for children, their parents will have to receive balanced and extensive information on the relevant benefits and risks. This thesis will discuss negative effects of epilepsy surgery focusing on unexpected adverse surgical and neurological outcome after epilepsy surgery procedures and invasive diagnostic procedures.

Epilepsy

According to the 2005 definition by the International League Against Epilepsy (ILAE), epilepsy is a "disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences this condition."[2] The predisposition is manifested by at least two spontaneous seizures or a comparably increased risk for future episodes.[3]

Seizures are unpredictable and may, depending of the seizure type, lead to loss of consciousness, falls, and injuries. The ILAE definition also highlights that the state of health for many persons with epilepsy is affected at least as much by the indirect consequences of the seizures and comorbid conditions as by the seizures themselves.[2] Although many people with epilepsy cope well with the disorder, frequently reported problems are adverse effects from antiepileptic drug (AED) therapy, cognitive symptoms, depression, and anxiety. There may be difficulties related to work, education, or driving, and experiences of reduced independency, isolation, and stigma.[2; 4-8]

Two-thirds of people with epilepsy become seizure-free with AED treatment.[9] The probability of long-term seizure freedom falls with the number of failed AED therapies. Of patients who become seizure-free, 90% have been reported to achieve this with their first or second therapy.[10] Based on such data, the ILAE has defined drug-resistant epilepsy as the failure of at least two adequate trials of tolerated AED schedules.[11]

Compared to patients who become seizure-free, patients with recurrent seizures have a higher risk for depression, anxiety disorders, cognitive symptoms, and increased mortality due to trauma, suicide, or sudden unexpected death in epilepsy (SUDEP).[7; 12; 13] Furthermore, frequent seizures can cause progressive developmental delay in infants and small children.[14; 15]

Epilepsy surgery

Epilepsy surgery is a neurosurgical treatment option for selected patients with drug-resistant epilepsy. Resective epilepsy surgery works by removing targeted brain networks or part of networks that are necessary for seizure generation, and has the potential to render the patient seizure-free.[16-18] Disconnective procedures isolate pathways that are important for the propagation of seizure activity and aim to reduce seizures or seizures of a specific type, such as callosotomy for traumatizing drop attacks.[19]

The decision to offer epilepsy surgery can often be based on clinical evaluation and a number of non-invasive investigations. The aim of this work-up is to define comorbidities, to identify the area responsible for the generation of the seizures, and to assess the risks of a surgical procedure. If a resective procedure is proposed, the resection volume has to be delineated from eloquent cortex, e.g., parts of the cortex that are essential for language and motor function.[20; 21]

Magnetic resonance imaging (MRI), long-term video-EEG monitoring (LTM), and neuropsychological investigations form the basis of presurgical investigations.[22; 23] Further modalities are indicated in special situations, e.g., when MRI is negative or inconclusive. For instance, positron emission tomography (PET), magnetencephalography (MEG), and subtraction ictal single-photon emission computed tomography co-registered to MRI (SISCOM) are used to localize the seizure onset, while functional MRI (fMRI) and diffusion tract imaging (DTI) aid in evaluating the risk for postsurgical deficits.[21; 24; 25]

In a proportion of presurgical evaluations, non-invasive investigations are insufficient to define the epileptogenic zone or its relation to eloquent cortex. In these cases, invasive diagnostic procedures may provide the information needed to proceed to surgery.[21; 26] Most of these are invasive electrode procedures, in which LTM is recorded with intracranial electrodes, thereby overcoming some of the limitations in anatomical accessibility and spatial resolution inherent in scalp registrations.

There are no clear evidence-based criteria for deciding which patients will benefit from invasive procedures. Since they carry a risk in themselves, they should only be performed when non-invasive data are insufficient for suggesting a therapeutic procedure but there are reasonable hypotheses about the localization of the epileptogenic zone.[21; 26]

Barriers to epilepsy surgery

Evidence from randomized controlled trials (RCT) supports superior efficacy of epilepsy surgery compared to AED treatment alone.[16-18] Consensus guidelines therefore recommend that patients with drug-resistant epilepsy, regardless of their age, should be referred promptly to specialized centers for evaluation for epilepsy surgery or other advanced treatment options.[14; 27] There are evidence-based criteria to help clinicians to identify patients who are suitable for referral.[28]

Despite this, surgical treatment is underutilized in many countries with different resources and public health care systems.[29-34] Although there may be a slow increase in the number of surgeries at least in Europe,[35; 36] disease durations of 10-20 years from the onset of epilepsy to surgical treatment are still common.[29; 35; 37]

In some countries, patients may be less likely to have surgery depending on socioeconomic factors such as ethnicity or insurance status.[38; 39] Attitudes towards epilepsy surgery among primary care physicians, general neurologists, patients, and families may also influence the time to referral. Referring physicians may have insufficient knowledge about the outcomes of surgery or the proper indications for surgical evaluation, leading to non-referral of suitable surgical candidates.[31; 40; 41] Patients may decline referral because they overestimate the risks of surgery.[42-46] Further factors shown to negatively influence patient acceptance for presurgical evaluation are lower seizure severity and higher age.[43]

Experienced centers with up-to-date knowledge of epilepsy surgery procedures and outcomes have the best qualifications to discuss the patient's expectations and relevant treatment options. Guidelines therefore stress referral for broad specialist evaluations of drug-resistant epilepsy as opposed to referral specifically for surgical therapy.[30]

Counseling before surgery

Opting for epilepsy surgery is an individual decision and patients weigh benefits and risk differently due to varying priorities.[47; 48] Up to 40% of those who undergo presurgical evaluations decline to undergo surgery or further invasive investigations.[47; 49] The reasons for this are not well known, but some studies suggest that perceptions about seizure severity, risk, and the likelihood of seizure-freedom are important factors also in this part of the process.[47; 49-51]

The optimal number of surgeries however depends on multiple issues. All factors cited as reasons for not referring to or conducting presurgical evaluations are important to consider when deciding for or against surgery.[52] Opting out from surgery can be an adequate decision. The primary goal is not to increase the number of surgeries but to reduce barriers for patients to receive proper evaluation and tailored counseling about the relevant treatment options. Information from the surgical team may reduce patients' worries about potential surgical adverse effects.[53] Acceptable harm is important to discuss when worsening of a neurological function is expected as the result of the procedure.[54] Balanced information must also take into account the alternative risk, i.e., the risks of continuing seizures.[1; 23; 55; 56]

Little is known about patient perspectives on the counseling process. One focus group study of patients who had undergone temporal lobe resection (TLR) reported that patients requested both individualized risk statistics and being able to share testimonials from patients who have positive or negative outcomes of the same procedure. [57] A limitation in this study was that all patients had favorable outcomes of surgery. Qualitative studies including patients who experience unchanged or worsened seizures or neurological sequelae could be used to improve counseling strategies and postoperative support.

Surgical quality assessment

Besides to provide information to patients and families, positive and negative outcome data are needed to ensure surgical quality. Prognostic factors allow surgical teams to identify patients at risk for negative outcomes and in some cases initiate supportive measures. Detailed prevalence data on specific complications enable comparisons between different surgical procedures and epilepsy surgery centers and may prompt improvements in procedures and perioperative routines.[58; 59]

Clear definitions of outcomes are important for comparisons between different studies including meta-analyses.[60; 61] A Cochrane review of epilepsy surgery found that half of included studies lacked detailed information on adverse effects. Moreover, many of the studies that reported adverse effects did not specify whether events were only perioperative or resulted in transient or permanent symptoms.[62] Other reviews highlight marked variations in reported complications rates which are likely to be influenced by variations in definitions and study methodology.[63-65]

Aims

Detailed information on negative outcomes of epilepsy surgery is necessary for patients and families to make informed decisions about treatment and for surgical quality assessments. The overall aim of this thesis was to analyze surgical and neurological adverse effects of epilepsy surgery and of invasive diagnostic procedures used in the preoperative evaluation for epilepsy surgery. Specific aims for the different studies were the following:

- **I.** To analyze complications related to invasive diagnostic evaluations with subdural or depth electrodes.
- **II.** To analyze complications related to therapeutic epilepsy surgery.
- **III.** To analyze the risk for increased seizure frequency or new-onset tonic-clonic seizures after therapeutic epilepsy surgery.
- **IV.** To propose and evaluate an evidence-based protocol for reporting complications related to invasive diagnostic procedures and epilepsy surgery.

Outline

The thesis is outlined as follows:

- **Outcomes of epilepsy surgery** gives a brief overview of the benefits and risks of epilepsy surgery as regards seizures, quality of life, social outcomes, and adverse effects.
- **Invasive diagnostic procedures** presents Paper I and reviews adverse effects related to invasive procedures used in the preoperative evaluation for epilepsy surgery, with a focus on invasive electrode procedures.
- **Epilepsy surgery procedures** presents Paper II and reviews adverse effects of resective, disconnective, and minimally invasive procedures for the treatment of epilepsy.
- **Epilepsy surgery failure** presents Paper III and discusses unfavorable seizure outcomes after epilepsy surgery, especially seizures that are increased in frequency or worsened in presentation.
- **Prevention of adverse effects** is a brief discussion of potential strategies used to reduce the rate of complications in epilepsy surgery and invasive procedures.
- **Methodological issues** discusses study designs and definitions in existing publications and proposes possible improvements in the reporting of complications, which were presented in Paper IV.

Outcomes of epilepsy surgery

Balanced information before epilepsy surgery requires equal consideration of the benefits and risks of the procedure as well as the risks of persistent seizures. Aims beyond seizure freedom are frequently reported by patients who consider epilepsy surgery and by their families. Evidence-based outcome data are necessary to set realistic expectations.

Patients' expectations from surgery

Qualitative studies of patients' expectations show that a primary goal for patients who consider epilepsy surgery is to achieve freedom from seizures or at least a significant reduction in seizures.[53; 66] Given the negative consequences of epilepsy, patients unsurprisingly also have hopes to improve their general well-being beyond seizure freedom. Goals frequently reported by patients are being able to wean AED therapy and to have a "normal life", meaning for instance to be able to work or go to school, drive, and socialize.[53; 66; 67] Some patients further hope to improve in self-esteem, mood and cognition.[66]

Seizures

Three RCT have shown that epilepsy surgery is superior to AED treatment alone in patients with drug-resistant epilepsy.[16-18] Two of these studied TLR in adults and adolescents,[16; 17] while the third more recent study investigated a wider range of procedures in children.[18] At short-term follow-up (one or two years after surgery), the proportions of seizure-free patients were reported to be 58-77% in the surgery groups compared to 0-8% in the medical groups.[16-18]

The numbers of included patients in the RCT are limited, with a total of only 234 patients randomized to either treatment arm. Of the 112 surgically treated patients, 62% had TLR.[16-18] Evidence from RCT therefore has to be complemented with data from observational studies. Several systematic reviews of controlled observational studies of various procedures confirm that seizure outcomes with epilepsy surgery are superior to with medical management alone.[62; 68-71] For TLR, outcomes in prospective observational studies have been shown to be comparable to the results reported in RCT.[72]

In other publications, there are marked variations in reported seizure-free rates, and surgical procedures, patient ages, and etiologies differ between studies.[73] Seizure freedom is often defined as absence of seizures with impairment of consciousness during the year preceding follow up. Using this definition, the overall seizure-freedom rate one year after surgery is about 60%.[62] In mesial temporal lobe epilepsy and epilepsy due to focal cortical dysplasia, short-term seizure freedom can be achieved for up to 80% of patients, and in extratemporal epilepsies of various etiologies up to 60%.[74] There is a high probability of seizure freedom, about 80%, for resection of well-circumscribed epileptogenic lesions such as cavernous hemangiomas and low grade tumors regardless of their location.[37]

Seizure outcomes are not static. In long-term follow-up, a minority of the patients who attain short-term seizure freedom have recurrent seizures or fluctuating patterns of remission and recurrence.[75; 76] Ten years after resective surgery, 40-50% of patients have been continuously free from seizures with impairment of consciousness since surgery.[77]

An understudied outcome is worsening of seizures, which has been reported in a small percentage of patients after epilepsy surgery.[78]

Antiepileptic drugs

There is no consensus on the optimal time point for reducing AED in patients who become seizure-free after surgery. In children, AED therapy is often reduced early in order to optimize cognitive outcomes. In adults, social issues such as driving may lead to a more hesitant approach towards reducing AED.

In a Swedish long-term study, the proportion of seizure-free patients who were off AED increased over time to reach 43% after ten years among adults and 86% among children.[76]

Mortality

Patients with epilepsy have increased mortality because of comorbid neurologic disorders, status epilepticus, lethal injuries, suicide, or SUDEP.[79] The risk of SUDEP is increased with persistent seizures, especially with a high frequency of tonic-clonic seizures (TCS).[13]

There are indications that successful epilepsy surgery reduces mortality in treated patients, although firm conclusions are hampered by different outcome measures and comparisons in the relevant studies.[80]

Single center studies report that surgically treated patients have lower mortality than patients who do not have surgery,[81] that seizure-free patients have lower mortality than patients with seizures after surgery,[81-83] and that patients with frequent TCS after surgery have higher mortality than patients with few or no TCS.[81] Similarly, population-based studies have reported non-significant trends towards lower mortality among surgically treated patients compared to controls without surgery, and among surgically treated patients who are seizure-free compared to patients with persisting seizures.[80]

Cognition

Cognitive symptoms are common in drug-resistant epilepsy. Up to 80% of surgical candidates have some preoperative impairment detectable in neuropsychological testing.[84]

Cognitive outcomes after surgery have been most studied for TLR. It was discovered early in the history of epilepsy surgery that patients who had bilateral hippocampal resections for epilepsy or psychiatric indications suffered severe anterograde amnesia. This was not seen with unilateral resections, unless there was an unexpected lesion on the contralateral side.[85; 86]

More subtle memory impairments can be demonstrated in neuropsychological testing. Deficits are commonly not noticed by the patients, and the correlation between subjective symptoms and objective function is surprisingly weak.[87] Unilateral hippocampal resections lead to worsened verbal memory in 20-30% of the cases, while improvements are less frequent.[87] Risk factors for significant worsening are dominant side resection, higher preoperative function, higher age at surgery, and presence of TCS before surgery.[88-90] Mild naming difficulties are common after dominant side resections, whereas impairment of visual memory can be seen with both right- and left-sided TLR.[87]

Cognitive outcomes are less well studied for children, but improved function appears to be more common than for adults, especially with reduction of AED therapy and in epileptic encephalopathies. Even with unchanged postoperative results, surgery may stop further cognitive decline and lead to improved function for treated children compared to controls.[87; 91]

Social outcome

Penfield and Paine remarked in the 1950s that the threat of loss of employment was a frequent motivation to undergo surgery, and vocational improvement was indeed seen in a significant proportion of treated patients.[1]

In a recent prospective register-based long-term study, the authors found no overall gain as regards employment in patients who had epilepsy surgery compared to the general population. However, subgroups of the cohort had better outcome. Previous employment, favorable seizure outcome, and younger age were strong predictors for being employed at any time point after surgery.[92]

According to the same study, the majority of patients who were employed five years after surgery also had the ability to drive, defined as being seizure-free and having a driver's license.[92] However, driving depends also on other factors, for instance economic resources and having intact visual fields, and these aspects have not been researched systematically.

Some patients who become seizure-free describe difficulties in adjusting to the new situation, the "burden of normality", which may affect social and psychiatric function.[23]

Psychiatric outcomes

In patients with drug-resistant epilepsy, psychiatric comorbidities have been reported in as much as 40-60% of the patients, even more in children.[7] Changes in psychiatric status are frequent after surgery, but causal relations are often unclear since a thorough preoperative assessment is not always at hand.[93] It is important that patients have adequate support from the surgical team in order to identify and treat psychiatric symptoms.[23; 93]

Depression and anxiety is reported in up to 40% after TLR, especially in patients with previous psychiatric symptoms.[7] Postoperative psychosis is reported to occur in 2% of patients without previous episodes.[93] Most psychiatric symptoms remit within the first year of surgery. Patients who become seizure-free have a lower risk of developing postoperative psychiatric symptoms, and those with preoperative depression may even improve after surgery.[7]

Surgical and neurological adverse effects

Like all major surgical procedures, epilepsy surgery carries risks related to anesthesia, the surgical procedure, or postoperative immobilization. In a Cochrane review of epilepsy surgery, the estimated rate of transient adverse effects was 6%, and of permanent adverse effects 7%. However, it was not specified in this review whether the adverse effects were expected or unexpected, and the cut-off for permanent symptoms varied between the included studies.[62]

Preoperative invasive investigations can result in both surgical and neurological complications, which are important to consider as they are diagnostic procedures which will not in themselves affect seizure outcome. This is especially important for the proportion of patients who do not proceed to surgery after invasive investigations.

Patient satisfaction and quality of life

As expected, seizure freedom is the major determinant of patient satisfaction following epilepsy surgery. However, most patients consider epilepsy surgery beneficial overall regardless if they become seizure-free or not.[94] Postoperative cognitive or neurological problems may contribute to dissatisfaction with or without satisfactory seizure outcomes.[1; 53]

In measures of health-related quality of life, adults who have epilepsy surgery improve in most domains compared to before surgery.[69; 95] As for patient satisfaction, the major predictor for improved quality of life is seizure outcome. Most studies indicate that improvements are more likely with complete seizure freedom compared to less than complete seizure freedom, although a recent study has questioned this.[96] Cognitive worsening affects quality of life negatively at group level, especially for patients who are not seizure-free.[95] Therefore, it is important to identify patients who are at risk for cognitive worsening without seizure improvement.[97] The impact of surgical or neurological complications on patient satisfaction or health-related quality of life has not been systematically investigated.[98]

One meta-analysis found that children who have epilepsy surgery improve in health-related quality of life compared to their preoperative status and compared to controls, especially if they became seizure-free.[99] Parents of children who had undergone epilepsy surgery reported improved quality of life compared to before their child's operation.[100]

Conclusions

Epilepsy surgery reduces seizures, improves quality of life, and probably reduces mortality in drug-resistant epilepsy, while social outcomes and outcomes regarding AED withdrawal are more variable. Cognitive and neurological adverse effects may affect patient satisfaction negatively even if seizure freedom is achieved.

Invasive diagnostic procedures

This chapter discusses Paper I and aims to give an overview over the literature on surgical and neurological adverse effects of invasive diagnostic procedures in the preoperative evaluation for epilepsy surgery.

Invasive electrode procedures

LTM with scalp electrodes is central in presurgical evaluations in order to record the patient's clinical episodes, confirm their epileptic nature, and localize their onset.[101] Invasive electrode procedures are specialized evaluations which are planned individually guided by previous investigations including LTM. In invasive procedures, electrodes are placed surgically to increase spatial and temporal resolution, reach areas not accessible for scalp registrations, and evaluate the relationship of the epileptogenic zone to eloquent cortex.[26]

Non-invasive video-EEG monitoring

Non-invasive LTM carries certain risks which are also seen during registrations with invasive electrodes although they are seldom reported among complications of invasive electrode procedures. Patients who undergo LTM are at risk for adverse events because measures are often undertaken to increase the likelihood of seizures during admission. Such methods include AED withdrawal, sleep deprivation, hyperventilation, and photic stimulation.[102]

In total, adverse events have been reported in 7% of admissions for LTM and include falls, seizure-related injury, status epilepticus, medication-related adverse events, seizure clusters, cardiorespiratory complications, and postictal psychosis.[103] Though most seizure-related injuries are mild, falls with fractures and traumatic brain injuries occur.[104] SUDEP has been reported in rare cases (1.2 per 10,000 admissions), especially when supervision has been suboptimal.[105] Close observation is important for patient safety but can be stressful especially for patients with a history of anxiety disorders. Adverse psychiatric reactions occur during LTM both as a reaction to the circumstances related to admission and as a postictal phenomenon.[104]

There are guidelines concerning the indications and technical requirements for LTM but not for patient safety and other aspects of quality of care.[106-108] Practice points emphasize individualized assessments of seizure risk before admission, close monitoring of high-risk patients, and appropriate precautions in the patient environment.[109; 110]

Planning of invasive investigations

Invasive investigations are chosen and planned based on all previous investigations, including clinical history, imaging, and a detailed analysis of ictal and interictal patterns recorded in non-invasive LTM. This analysis results in a one or more hypotheses about the location of the epileptogenic zone and its relation to eloquent cortex.[26; 111]

Regardless of the implantation method, each invasive electrode samples only a small part of the brain, and suboptimal placement can lead to the failure to delineate a possible resection volume or an inappropriate resection. Invasive investigations should not be used for explorative purposes or, because of the additional risk with these procedures, in cases where the surgical plan is unlikely to be changed after investigation. Bilateral implantations are rarely indicated.[26; 111]

Subdural explorations (SDE) and stereo-EEG (SEEG) are the most common invasive investigations. They have specific advantages and disadvantages and can be considered as complementary.[26; 111; 112] Historically, epilepsy centers have often pursued just one modality based on tradition and individual preferences, with SEEG being predominant in France, Italy, and in some Canadian centers, while SDE have been used in other centers, notably in the US.[113] During the last decade, SEEG has been introduced in many centers around the world, facilitated by advancements in neuronavigation and angiographic planning.[112; 113]

SDE involve the placement of electrodes in the subdural space, which allows a dense coverage of superficial cortical areas. The electrodes come in rectangular arrangements of various sizes called grid electrodes and linear arrays called strip electrodes. Grids must be placed through open craniotomy, while strips are inserted either through a craniotomy or a burr hole.[114] Electrical stimulation mapping allows very precise localization of cortical functions.[26] SDE is therefore especially suited to define the exact relationship between a superficial lesion and eloquent cortex.[113; 115]

Grids and strips are frequently used in combination. Sometimes they are also complemented with a limited number of intracerebral (depth) electrodes in order to record deep foci such as the hippocampus or the depths of sulci.[26]

Subdural strips can be used in isolation. In these cases, the electrodes are inserted blindly through burr holes, which avoids craniotomy but limits anatomical precision. The most frequent indication is to lateralize temporal lobe seizures. Several strips can be inserted in different directions through the same burr hole to cover different part of the temporal lobes, especially the basal aspects and the temporal poles.[113; 114; 116; 117]

SEEG is a distinct method which was developed by Talairach and Bancaud in Paris in the 1950s. The term stereo-EEG refers to the three-dimensional view of the epileptogenic network underlying the method.[118] SEEG electrodes are intracerebral electrodes most often placed through twist drill holes. The absence of direct visual control at the insertion point is compensated by meticulous angiographic planning. The electrode trajectories are highly individualized to make possible testing of electro-clinical hypotheses about the patient's seizure patterns and typically involve a fairly high number of electrodes.[118; 119] Traditionally, frame-based stereotactic systems have been used to place the electrodes, but most centers today prefer frameless, neuronavigation-based systems.[118]

Specific indications for SEEG include possible involvement of deep-seated regions such as the insula, operculum, and depths of sulci, previous SDE, the need of extensive bilateral coverage, and MRI-negative epilepsy.[120-122] Direct electrical stimulation of SEEG electrodes can be used for functional mapping and also helps to assess the role of a specific region in the patient's seizure patterns.[123] The main limitations of the method are its sampling bias and imprecise localization of speech areas compared to SDE. Furthermore, small children and infants cannot undergo SEEG because their skull bone is not thick enough to secure the electrodes.[122]

After both SDE and SEEG, about 80% of the patients proceed to a resective procedure,[124; 125] ultimately leading to seizure freedom for 50-65% of those who have surgery.[124-126] SEEG is resource intensive but has been shown to be cost-effective if increased seizure freedom in patients who can have surgery is considered.[127] Given the seizure-free rates in resected patients it is very likely that the same holds for SDE, although this has not been evaluated directly. Still, the risks with each method should not be neglected, especially as some centers report an increasing proportion of invasive procedures which are not followed by resective surgery.[128]

Although few centers choose actively between the two methods, it should be noted that the risk of complications is generally lower in SEEG compared to SDE, as documented in a systematic review and meta-analysis of studies with either modality[125] and single-center cohorts comprising both modalities.[129; 130] SEEG is also more tolerable as measured by the need for narcotic analgesics during the postoperative period.[130]

Subdural explorations

In Paper I, we analyzed complications related to invasive electrode procedures performed in Sweden 1996-2010 (Table 1). We extracted data on surgical and neurological complications from the Swedish National Epilepsy Surgery Register (SNESUR), which collects prospectively reported data from the six Swedish epilepsy surgery centers. Complications were defined as unwanted, unexpected, and uncommon events after a procedure. Minor complications are defined in SNESUR as those that resolve within three months, while major complications affect activities of daily living (ADL) and last longer than three months. Major complications also include any significant neurological deficits, even if they do not affect ADL.[131]

There were 271 procedures, 90% of which were SDE. In total, there were complications in 13 procedures (4.8%), none of which were major. A previous publication from SNESUR reported complications related to invasive electrode procedures performed 1990-1995. Of 205 procedures, 84% were SDE. There were 13 (6.3%) minor and no major complications.[131]

There was no mortality in these studies. Of note, both studies reported potentially life-threatening hematomas which prompted emergency evacuation. These complications were classified as minor complications according to the definition because there were no permanent sequelae. The combined series 1990-2010 comprised 17 subdural or epidural hematomas. Eight of these required surgical evacuation, seven with grids and one with strips. Other studies report the need for evacuation in up to 3% of implantations.[63] Close personal supervision throughout the monitoring period is necessary to prompt interventions and avoid development of permanent symptoms.[132; 133]

Further results from Paper I are summarized in Table 1 along with the results reported in three meta-analyses.[63; 125; 126] The percentages taken from Paper I are given in relation to the whole cohort, which includes about 10% of non-SDE procedures. The systematic reviews vary in methods and criteria for study selection. Although focused on SDE, studies with various modalities were included in the systematic reviews if the majority of implantations were SDE. Some studies lacked details on electrode types, limiting the precision in data extraction. The definition of adverse events varied markedly between the included studies, which explains a range of 0-57% in reported morbidity rates.[125]

According to the meta-analyses, the total rate of hemorrhage in SDE is 3.7-10.7%, with significant variations in the underlying studies. In a retrospective study of 317 SDE implantations, Schmidt et al. reported postoperative radiologic abnormalities including asymptomatic findings in 50.5%, while symptomatic complications were seen in 9.1%. One subdural hematoma (0.3%) required emergency evacuation. The majority of the asymptomatic findings were intracranial fluid collections (19.6%) and hemorrhage (16.4%).[134] Another frequently asymptomatic finding is cerebral infarction, which has been reported to be more common with grid explorations compared to strips.[135]

The reported rate of CSF leakage varies between studies because transient leakage is often considered as an expected adverse effect as opposed to a complication (so also in Paper I).[133; 134; 136] In some cases, however, surgical intervention is indicated because of persistent CSF leakage.[63]

For isolated strips, we reported a 2.2% rate of minor complications compared to 7.4% in grid explorations (p=0.067; Paper I). In the previous report from SNESUR, 3.8% had complications with strips compared to 14.2% with grids (p=0.026).[131] If the cohorts are combined, there was a significantly lower risk for complications associated with strips (3.0%, N=265) compared to grids (9.3%, N=150; p=0.01). The low morbidity with strips compared to grids confirms the findings of other studies.[134; 137]

Table 1. Complications related to subdural registrations reported in Paper I and systematic reviews.

	Paper I	Arya et al. 2013[63]	Sacino et al. 2019[126]	Yan et al. 2019[125]
No. of included studies	—	21	14	22
No. of included patients	271	2,542	697	1,994
Mortality	0	0.2%	0	0.4%
Any complication	13 (4.8%)	—	—	15.5%
Major complications	0	—	—	—
Minor complications	13 (4.8%)	—	—	—
Any intracranial hemorrhage	10 (3.7%)	4.0%	10.7%	4.8%
Intracerebral hemorrhage	0	—	—	1.4%
Subdural hemorrhage	7 (2.6%)	—	—	3.4% (including epidural)
Epidural hemorrhage	3 (1.1%)	—	—	—
Any infection	2 (0.7%)	—	10.8%	1.6%
Meningitis or abscess	0	2.3%	—	2.1%
Wound infection	2 (0.7%)	3.0%	—	1.0%
CSF leakage	0	12.1%	11.9%	0.6%
Brain edema	0	2.4%	—	—
Transient neurological deficit	0	4.6%	—	5.7%
Permanent neurological deficit	0	—	—	0.3%
Electrode dislocation	1 (0.4%)	—	—	—
Lead fracture	0	—	—	1%
Medical complications	—	—	—	2.6%

Depth electrodes

Complications related to depth electrodes are difficult to isolate in the context of a combined implantation scheme.[138; 139] Depth electrodes have been used in more or less standardized arrangements for bilateral occipito-temporal implantations, either in isolation or combined with strips, but this method has been abandoned in most centers.[138; 140-142]

The most ambitious study of different electrode types in combined implantations is the above-mentioned retrospective study of 317 SDE, where 316 of the implantations involved strips, 105 grids, and 159 depth electrodes.[134] All patients had postimplantation CT or MRI. The authors attempted to ascribe all postoperative abnormalities to a specific electrode based on the proximity of the finding to the nearest electrode. Significantly more abnormal findings were associated with subdural (47.9%) compared to depth electrodes (25.2%), but there was no significant difference in the rate of clinically significant complications related to subdural electrodes (9.1%) compared to depth electrodes (6.3%). However, complications related to depth electrodes could be overestimated, as the authors ascribed all complications with unclear relation to a specific electrode to both electrode types, which was the case for all clinically significant complications related to depth electrodes.[134]

In Paper I, we reported data according to the electrode type most prone to complications. Hence, data regarding depth electrodes were only presented for isolated depth explorations. There was one complication in 14 intracerebral depth explorations (one electrode dislocation). The previous cohort included two implantations without complications,[131] giving a total of 6.3% complications. These data are too limited to allow conclusions.

Stereo-EEG

The SEEG method was not used in Sweden during the time period studied in Paper I. Adverse effects have been investigated in several systematic reviews with variations in primary endpoints, selection criteria, and methods for computing prevalence rates (Table 2).[118; 125-127; 143] Methodological issues in the underlying studies were inconsistent reporting of sample sizes, lack of data on specific outcomes, or the failure to clarify whether a complication was absent or just not reported.

Despite this, complication rates are fairly consistent in the systematic reviews. The mortality rate is 0.1-0.3% and amounts to a total of five reported cases, related to intracerebral hemorrhage (two cases), ventriculography performed as part of the surgical planning (two cases), and cerebral edema due to severe hyponatremia.[118; 143] Ventriculography has been abandoned in preoperative planning and the mortalities related to this procedure were reported in a very early publication.[118]

Permanent neurological deficits are reported in 0.2-1%.[125; 127; 143-145] Almost all permanent symptoms are caused by intracranial hematomas, but transient neurological deficits can occur with edema close to eloquent cortex.[144]

The reported rate of hemorrhage ranges from 0-5%, with a likely bias for symptomatic cases.[121; 126; 146] Asymptomatic bleedings are common, and many centers do not routinely perform postimplantation imaging.[147] In a series of 549 SEEG implantations in a single center, a complete series of postimplantation CT scans were retrospectively reviewed by a neuroradiologist blinded to clinical data. In this study there were 105 (19.1%) hemorrhages, 12 (2.2%) of which were symptomatic.[144]

One study reported unspecific adverse events not counted as complications, comprising sporadic headache (55.6%), transient low-grade fever (5.6%), and systemic infection (5.6%).[148]

Table 2. Complications related to SEEG reported in systematic reviews.

	Mullin et al. 2016[143]	Cardinale et al. 2016[118]	Garcia-Lorenzo et al. 2019[127]	Sacino et al. 2019[126]	Yan et al. 2019[125]
No. of publications	30	359	33	9 (pediatric only)	17
No. of patients	2,624	Ca. 4,000	2,959	277	1,992
Mortality	0.3%	0.1%	0.19%	0.3%	0.2%
Any complication	1.3%	0.9% ("major" only)	1.3%	—	4.8%
Hemorrhage	1.0%	0.4%	2%	2.9%	4.4%
Intracerebral hemorrhage	0.7%	0.4%	1%	—	2.3%
Subdural hemorrhage	0.4%	—	1%	—	0.7%
Infection	0.8%	0.2% (intracranial only)	1%	0	0.9%
Cerebral abscess	0.9%	—	1%	—	0.7%
Superficial wound infection	1.4%	—	1%	—	0.2%
Meningitis	0.6%	—		—	0.1%
Permanent neurological deficit	0.6%	—	1%	—	0.2%
Status epilepticus	0.3%	—	—	—	—
Malfunction of electrodes	0.4%	—	—	—	—
Malposition of electrodes	0.6%	—	—	—	—
Other	1.1%	—	—	—	—

Other invasive EEG procedures

A few more rarely pursued modalities have been proposed to increase the yield of non-invasive LTM by means of surgically placed electrodes which do not require a craniotomy or burr hole.[26]

Foramen ovale electrodes

Foramen ovale electrodes are inserted under fluoroscopy guidance into the ambient cistern. They are designed for the evaluation of temporal lobe epilepsy and provide a more precise registration of the mesial aspects compared to scalp registrations, although the coverage of the anterior temporal lobes is limited compared to SDE and SEEG.[26]

Two small case series reported 2.2-2.6% complications, including local cheek hematoma, failure of the electrodes to reach their target, and facial pain.[149; 150] In a larger series of 331 implantations, there were 6.6% complications, including cheek edema, paresthesia, dislocation of the electrode, and intracranial hemorrhage. No permanent deficits developed.[151] In Paper I and in the previous report from SNESUR,[131] only 22 foramen ovale explorations were reported with no complications.

Epidural registrations

Epidural peg electrodes are placed through a twist drill hole with the tip reaching the epidural space. Because the electrodes only record from the convexity, epidural pegs are almost exclusively used as a part of an implantation scheme comprising also subdural and/or depth electrodes. A significant risk of infection has been reported.[26]

Few registrations with epidural electrodes have been reported in SNESUR. In Paper I, we reported two implantations without complications, and the previous reported counted two minor complications (both infections) in 17 implantations, giving a total complication rate of 10.5%.[131]

The Wada test

The Wada test stands out among invasive investigations in that it is not used for recording seizures but for evaluating the risk for neurological worsening after resection. It uses a selective intracarotid injection of a fast-acting anesthetic to inhibit one hemisphere temporarily, which allows functional assessment of the contralateral hemisphere in isolation.[152]

The Wada test has been the gold standard for evaluating the risk for aphasia and to a lesser extent amnesia after TLR but has largely been replaced by functional MRI (fMRI), which is non-invasive and also allows anatomical localization.[35; 153] However, the Wada test is listed among the procedures to report in the protocol proposed in Paper IV as some centers still conduct it if fMRI is not feasible or its findings inconclusive.[153; 154]

The Wada test has a specific adverse effect profile which has been described in several observational series and studies comparing different anesthetics.[155-159] The major risk comes from the cerebral angiography with in itself carries a risk of neurological complications of 0.3-2.3%.[159] The administration of an anesthetic may cause additional adverse effects which may depend on the selected agent.[159]

Risk factors

Intuitively, it is likely that more extensive implantations carry a higher risk for complications because of larger craniotomies, larger mass effect, a higher number of burr holes, or a higher number of electrodes passing through the brain parenchyma. Studies have used different measures to assess the influence of this factor on the rate of complications.

In a meta-analysis of SDE, a higher number of electrode contacts was found to be associated with increased frequency of adverse events.[63] In single-center studies, complications have been reported to be associated with the number of electrode cables,[160] the number of electrode contacts,[137; 161; 162] the number of grids,[137; 162] the size of grids,[133] the number of burr holes,[137] the number of trepanations,[137] the number of electrode cable exit sites,[160] and the number of added depth electrodes.[139] One study found no correlation between number of strips and complicatons.[134]

In SEEG, some studies have reported a correlation between complications and the number of electrodes,[144; 147] or the number of implanted lobes.[147] The cut-off for "too many electrodes" is not known. One study reported a sensitivity analysis, according to which the statistically optimal threshold for hemorrhage risk, 13 electrodes, had only moderate specificity and sensitivity.[144]

Longer duration of monitoring has been associated with increasing number of adverse events in SDE[63; 160; 162] and with foramen ovale electrodes,[151] but not in SEEG.[144; 147]

Since SNESUR does not contain information on the number of electrodes, size of grids, or the duration of monitoring, we could not analyze these potential risk factors in Paper I.

In Paper I, we reported a higher rate of complications in patients over 35 years of age, but the difference was not statistically significant. In studies of various invasive modalities, significant correlations between higher age and complications have been reported in some publications[155; 157; 162] but not replicated in other studies.[134; 147; 154; 163] Comorbidity is seldom analyzed as a predictor for complications. One study reported a correlation between hypertension and hemorrhage for various electrode implantations, including invasive diagnostic procedures and deep brain stimulation.[164]

Previous craniotomy has been indicated in some studies to be a risk factor for hemorrhage related to SDE.[132; 134] One report found a low rate of complications in patients who underwent repeat SDE, but this conclusion was not supported by direct comparison.[165]

One study reported a higher incidence of infections related to subdural grid implantations when the bone flap was explanted compared to when the bone flap was left in place.[166] This issue has not been investigated systematically in other studies.

Conclusions

Several studies indicate that more extensive implantations carry a higher risk of complications, both in SDE and SEEG. Therefore, individual electrodes should be implanted only if considered necessary for proving or disproving the surgical team's clinical hypothesis or otherwise for establishing a plan for the subsequent resection. Observational data show that complications are less common in SEEG compared to SDE. With careful supervision, complications leading to permanent symptoms are rare both with SDE and SEEG, and patients should be offered proper invasive investigations if likely to inform decisions about therapeutic surgery.

Epilepsy surgery procedures

This chapter presents Paper II and aims to review the surgical and neurological adverse effects of therapeutic epilepsy surgery. Complications of epilepsy surgery are similar in many aspects to those of other neurosurgical procedures. However, the risk of neurological worsening is particularly important to consider since epilepsy surgery is an elective treatment aiming to improve quality of life and most procedures are performed in patients without preoperative deficits.

General studies

In Paper II, we presented data from SNESUR regarding all 865 epilepsy surgery procedures performed 1996-2010. As for invasive investigations, complications were classified as major or minor. All neurological complications were classified as major if symptoms lasted more than three months. Surgical complications were classified as major if symptoms lasted more than three months and affected ADL.[131] In total, there were major complications in 3.0% and minor in 7.5%. The previously published cohort from SNESUR 1990-1995 comprised 3.1% major and 8.9% minor complications.[131]

Mortality

Major single center studies with 415-1,232 cases report a very low risk for mortality from epilepsy surgery of 0-0.1%.[147; 167-173] A large multicenter review reported 0.15% deaths after 2,611 procedures.[174] There was no surgical mortality in the 865 procedures performed in Sweden 1996-2010 (Paper II) or the 449 procedures performed 1990-1995.[131]

Three studies based on the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) report surprisingly high 30-day mortality rates of 1.4-3.4%.[175-177] One hypothesis was that the inclusion of low-volume and non-academic centers contributed to the high rate compared to reports from large-volume centers.[177] It could also be observed that 30-day mortality includes deaths unrelated to surgery and that the NSQIP samples were limited compared to the potential number of included cases.

Surgical complications

The rates for specific surgical complications in 865 epilepsy surgery procedures are listed in Table 3 (Paper II).

We reported infectious complications in 2.2% procedures, in one case (0.1%) classified as major complication as symptoms persisted beyond the three months follow-up. The reported complications were surgical site infections of various degrees of invasiveness. The rate of surgical site infections is comparable to the pooled prevalence in a systematic review and meta-analysis of resective epilepsy surgery published by Hader et al. (Table 3).[65] More generally, similar rates of 2.2-4.1% have been reported for adults and children who undergo elective neurosurgery.[178-180] The previous publication from SNESUR reported infections in 23/449 (5.3%).[131] The decrease is statistically significant (p=0.003), which may indicate improvements in perioperative management.

The rates of intracranial hematoma and hydrocephalus reported in Paper II were slightly lower compared to the aforementioned meta-analysis.[65]

The rate 0.5% of cerebrospinal fluid (CSF) leakage reported in Paper II was unchanged compared to the previously reported result from SNESUR, 0.7%.[131] This contrasts the meta-analysis, where 8.5% had this complication. The authors reported that the risk for CSF leakage was higher for children compared to adults and for extratemporal compared to temporal surgery, but the surgical panorama in the underlying studies was not described.[65] It is conceivable that in a higher proportion of children and patients with extratemporal epilepsy, resection was preceded by subdural registrations, which in themselves carry a risk for CSF leakage. However, the most likely explanation of the difference is that minor CSF leakage was not recorded in SNESUR due to the strict definition of complications as unwanted, unexpected, and uncommon events.[131]

Table 3. Surgical complications after epilepsy surgery reported in Paper II and a systematic review.

	Paper II (N=865)			**Hader et al. 2013[65]**
	Major	Minor	Total	Total (95% CI)
Infection	1 (0.1%)	18 (2.1%)	19 (2.2%)	3.0% (2.6-3.6%)
Pneumonia	—	—	—	0.7% (0.3-1.6%)
Aseptic meningitis	—	—	—	3.6% (2.6-5.1%)
Hematoma	2 (0.2%)	12 (1.4%)	14 (1.6%)	2.5% (2.0-3.2%)
Deep venous thrombosis/ pulmonary embolism	0	5 (0.6%)	5 (0.6%)	1.0% (0.6-1.6%)
Hydrocephalus	0	2 (0.2%)	2 (0.2%)	1.0% (0.6-1.8%)
CSF leakage	0	4 (0.5%)	4 (0.5%)	8.5% (6.5-11%)
Brain edema	0	1 (0.1%)	1 (0.1%)	—
Other	2 (0.2%)	—	2 (0.1%)	—
Total major	6 (0.7%)	—	—	1.5% (1.1-2.1%)
Total minor	—	42 (4.9%)	—	5.1% (4.5-5.8%)

Neurological complications

Neurological function after epilepsy surgery may depend on the preoperative status, the type and extent of surgery, and unexpected events. Unexpected worsening often occurs as the result of a surgical complication such as intracranial hematoma or infection, which affects critical white matter tracts, vascular anatomy, or eloquent cortex.[22] Focal resections within or in the proximity of eloquent cortex may result in neurological worsening, which is inherent to the procedure and discussed preoperatively with the patient. Such negative effects are not complications in the strict sense but rather expected adverse effects or sequelae.[131; 181]

In Paper II, we reported 2.8% major and 3.3% minor neurological complications, comparable to the previous report from SNESUR (1.8% and 2.6%, respectively)[131] and the pooled prevalence reported by Hader et al. (Table 4).[65] The most important differences between the SNESUR studies and the review is the inclusion of psychiatric and cognitive complications in the latter, and the strict definition of visual field complications in SNESUR. Minor visual field defects (VFD) are seen in 48-100% after TLR[182] and are hence not reported as complications in SNESUR but considered as expected.[131]

Table 4. Neurological complications after epilepsy surgery reported in Paper II and a systematic review.

	Paper II (N=865)			**Hader et al. 2013[65]**	
	Major N (%)	Minor N (%)	Total N (%)	Major (95% CI)	Minor (95% CI)
Hemi/monoparesis	12 (1.4%)	11 (1.3%)	23 (2.7%)	1.8% (1.5-2.3%)	3.3% (2.9-3.9%)
Sensory deficit	1 (0.1%)	2 (0.2%)	3 (0.3%)	—	—
Hemianopia	6 (0.7%)	1 (0.1%)	7 (0.8%)	2.1% (1.7-2.7%)	—
Minor VFD (quadrant or less)	—	—	—	—	12.9% (11.5-14.5%)
Cranial nerve deficit	4 (0.5%)	8 (0.9%)	12 (1.4%)	0.4% (0.2-0.9%)	2.1% (1.6-2.7%)
Dysphasia	2 (0.2%)	9 (1.0%)	11 (1.3%)	0.8% (0.5-1.3%)	3.7% (2.6-5.1%)
Other	1 (0.1%)	—	1 (0.1%)	—	—
Memory deficit	—	—	—	0.7% (0.4-1.1%)	5.1% (3.9-6.5%)
Psychiatric complications	—	—	—	1.9% (1.1-3.4%)	5.5% (4.4-6.8%)
Total	24 (2.8%)	29 (3.3%)	53 (6.1%)	4.7% (4.1-5.3%)	10.9% (10.1-11.7%)

Medical and anesthesiological complications

General peri- and intraoperative complications are seldom reported in epilepsy surgery series,[183; 184] which is indeed the case for surgery in general.[185] In Paper II, we did not include anesthesiological complications, for instance airway problems and electrolyte disturbances, unless neurological function was affected. No cases of major systemic infections were reported, probably because most patients were young with few comorbidities. Studies based on NSQIP report urinary tract infection in 1.5-2.5%, pneumonia in 0.5-1.5%, sepsis in 1-1.5%, unplanned reintubation in 2%, prolonged (>48 hours) ventilator dependency in 2.0%, myocardial infarction in 0.2-0.5%, and cardiac arrest in 0.5%.[175-177]

Focal resections

The majority of epilepsy surgery procedures are focal resections. Focal resections are often classified based on their lobar localization. In the following we will adhere to this traditional presentation, but it should be kept in mind that resections within one lobe comprise both limited lesionectomies and larger parenchymal resections.

Temporal resections

The majority of focal resections are TLR, comprising both small neocortical resections and more extensive procedures used to treat mesial temporal lobe epilepsy. Some studies report all TLR as one group while others specify procedures or etiologies or describe the results of a single surgical approach.[64]

The traditional procedure for mesial temporal lobe epilepsy is anterior temporal lobe resection (ATL) which involves resection of the anterior and lateral parts of one temporal lobe followed by resection of the mesial structures. Different approaches for selective amygdalohippocampectomy (SAH) which preserve cortex overlying the mesial structures are performed with similar seizure outcomes.[71]

In Paper II, we reported complications related to 523 TLR (122 in children). Of these, 332 included hippocampus, 169 excluded hippocampus, and 22 were SAH. In total, there were 15 major (2.9%) and 41 minor complications (7.8%). The complication rates were similar for procedures including or excluding hippocampus, but complications were more common in the few cases with SAH.

Table 5 shows the results from Paper II for all TLR along with a systematic review and meta-analysis of complications related to ATL by Brotis et al. which included 25 studies with a total of 2,842 patients.[186] The search strategy was dependent on MeSH (Medical Subject Headings) indexing for TLR and ATL, yielding unpredictable results for mixed surgical cohorts harboring cases with ATL (including Paper II) and cohorts comprising only SAH. Georgiadis et al. compiled a narrative review of a wider range of TLR studies.[64] Here, the authors did not attempt to compute pooled prevalences because of an extreme variation in reported complication rates due to heterogeneity in surgical techniques, definitions, and data collection. The total morbidity rates reported by Brotis et al. and Georgiadis et al. are not comparable to Paper II because they include psychiatric and cognitive complications and/or asymptomatic findings. Large retrospective single-center studies with 432-1,232 TLR where only surgical and neurological complications are considered report lower morbidity rates.[147; 168; 170; 171; 173; 187]

Some studies have reported that complications were more common with complete ATL compared to SAH,[169; 188] but other studies have found no difference in the rate of complications with different surgical approaches for TLR.[173] In contrast, we found in Paper II that the total complication rate was significantly higher in SAH compared to the other procedures (32% vs. 8.9%, p=0.0053). This result should be interpreted with caution due to the very small number of SAH but underscores the need for surgical experience with this procedure.[173] SAH may reduce VFD compared to ATL, but the interpretation is complex because the surgical approach appears to affect the extent rather than the incidence of VFD.[189; 190]

Table 5. Complications related to TLR in Paper II and two reviews.

	Paper II (N=523)		**Brotis et al. 2019[186]**	**Georgiadis et al. 2013[64]**
	Major	Minor	Pooled prevalence (95% CI)	Rate in reviewed studies
Mortality	0	—	1% (1-2%)	—
Infection	0	10 (1.9%)	3% (2-4%)	1.3-11.9%
Hematoma	1 (0.2%)	8 (1.5%)	2% (1-5%)	0.6-3.8%
Deep venous thrombosis/pulmonary embolism	0	5 (1.0%)	—	1.9%
Hydrocephalus	0	1 (0.2%)	2% (1-4%)	0.1-3.1%
Cranial fluid collections	—	—	2% (1-3%)	0.4-1.7%
Hemi/monoparesis	5 (1.0%)	4 (0.8%)	4% (3-6%; including sensory deficit and dysphasia)	0.9-8.5%
Sensory deficit	1 (0.2%)	1 (0.2%)	—	—
Dysphasia	1 (0.2%)	7 (1.3%)	—	0.6-7.7%
VFD	5 (1.0%)	0	6% (3-11%)	0.2-69%
Cranial nerve deficit	3 (0.6%)	6 (1.1%)	3% (2-5%)	2.1-19%
Other	1 (0.2%)	0	—	—
Total	15 (2.9%)	41 (7.8%)	17% (12-24%)	0-88%

Extratemporal resections

Extratemporal procedures are even more heterogeneous than TLR and comprise limited resections of a lesion visible on MRI and parenchymal resections of various sizes guided by invasive investigations in MRI-negative cases. Depending on the location of the resection and its relation to eloquent cortex, the rate of expected new postoperative neurological deficits can be as high as 30%.[191] In contrast, if only unexpected symptoms are reported, permanent morbidity (including surgical complications) is reported in 0-4.8% and transient in 5.8-10%.[191; 192]

In Paper II, we reported the complications related to 213 extratemporal lobe resections, 50% of which were performed in children. There was no significant difference between the rates for major complications or any complication for extratemporal lobe resections compared to TLR (3.9% vs. 2.8%, and 11.3% vs. 10.7%, respectively), which was also the case in the meta-analysis by Hader et al.[65] Tanriverdi et al. reported 5.4% complications for extratemporal resections compared to 2.9% for TLR.[147] Panighari et al. divided extratemporal procedures into eloquent and non-eloquent resections. Compared to 0.9% major and 3.9% minor complications for TLR, eloquent extratemporal surgery had 17.9% major and 25.4% minor complications, and non-eloquent extratemporal lobe resections had no major and 18.5% minor complications.[170]

In Paper II, we followed the previous report from SNESUR and counted complications per frontal, parietal, and occipital resections.[131] In 142 frontal lobe resections (69 in children), we observed 2.8% major and 7.1% minor complications, similar to reports from single centers (Table 6).[131; 147; 193-195]

Resections in the central (perirolandic) area carry a risk of damage to the primary motor and sensory cortices. Tanriverdi et al. reported 1.5% surgical, 1.4% major neurological, and 5.9% minor neurological complications, considering only unexpected worsening as a complication.[147] Other case series have reported any new or worsened neurological deficits whether this was expected from the procedure or not. Permanent deficits were seen in 0-70% depending on whether primary cortex was involved in the resection plan. The deficits were usually mild and considered as acceptable given favorable seizure outcomes.[196-199]

Table 6 shows the morbidity rates reported for parietal and occipital resections in Paper II and single center studies with varying definitions of complications. In a systematic review and meta-analysis of posterior resections, 28% of the patients had preoperative VFD, and 57% were reported to have new or worsened VFD compared to preoperatively. Other adverse effects were not evaluated.[200] In Paper II, there were 3 (6.8%) major and 5 (11.3%) minor complications in parietal resections, and 1 (3.7%) major and 1 (3.7%) minor complications in occipital lobe resections. Expected VFD were not complications according to the definition in SNESUR, while one case of transient hemianopia after a parietal lobe resection was considered as unexpected and hence as a complication.

The insula is frequently involved in temporal and extratemporal lobe epilepsies, but insular seizure onset is rare. Surgery is difficult due to the proximity to large vessels and the pyramidal tract. Insular resections are seldom reported as a separate category in major series, but small case series indicate that the majority of patients have transient neurological deficits, while permanent symptoms have been reported for 8-17%.[201; 202]

Table 6. Complications related to extratemporal resections.

	Paper I (N=213)		Single center studies
	Major complications	Minor complications	Total morbidity
Frontal lobe resections	4 (2.8%)	10 (7.1%)	5.2-17.1% [131; 147; 193-195]
Parietal lobe resections	3 (6.8%)	5 (11.3%)	13.2-39.5% [131; 147; 203; 204]
Occipital lobe resections	1 (3.7%)	1 (3.7%)	0-10.1% [131; 147; 205]
Total extratemporal resections	8 (3.8%)	16 (7.5%)	

Multilobar resections

Multilobar resections are sometimes used for treating cases with extensive epileptogenic pathologies, e.g., malformations of cortical development, gliosis after trauma or infection, and tumors.[206] Preoperative neurological deficits are common in this group of patients. In an American series, 19% had a VFD prior to surgery, and 24% had hemiparesis or monoparesis.[206] A Swedish study based on data from SNESUR 1990-2013 comprised 57 multilobar resections. Of these cases, there was a preoperative hemiparesis in 23%; in total, 33% of the patients had any preoperative deficit.[207]

The American study reported new or worsened VFD postoperatively in 19% of the patients, and a new or worsened motor deficit in 11%. Other adverse events were not reported.[206] In the Swedish study, there were 9% new neurological deficits, half of which were permanent. According to the definition in SNESUR, only unexpected worsening was considered as a complication. In total, major complications occurred in 5.3%, comprising one infarction of the middle cerebral artery, one epidural abscess, and one hemiparesis. Minor complications occurred in 17.5%, including wound infections, transient neurological worsening, shunt dysfunction, and CSF leakage.[207] One review mentions hydrocephalus and shunt-related craniosynostosis as potential complications in multilobar resections without providing percentages.[208]

Hemispheric procedures

Patients with epilepsy involving extensive unilateral hemispheric pathology and impaired contralateral motor function can be candidates for hemispheric procedures, where the basic goal is to isolate the pathological from the healthy hemisphere.[209; 210]

The first hemispheric procedures were anatomical hemispherectomies with resection of the entire hemisphere. This procedure conveyed a high risk of repeated hemorrhage into the operational cavity and subsequent hemosiderosis and hydrocephalus. Later, several techniques for functional hemispherotomy have been developed in which the vascularized pathological hemisphere is left functionally disconnected from the normal brain.[209; 210]

A systematic review and meta-analysis of all hemispheric procedures included 29 studies, 26 of which reported complications. In total, there was shunting for hydrocephalus in 14%, wound complications in 2%, hemorrhage or intracranial infection in 3.5%, and other complications in 10.6%. Overall mortality was 2.2%.[210]

Shunting is needed significantly more often after anatomical hemispherectomy compared to other hemispheric procedures.[210; 211] The overall mortality rate is reported to be 0.9-2.2%.[210; 212; 213]

Paper II reported 43 hemispheric procedures (40 in children) with no major and 4 (9.3%) minor complications. Hydrocephalus developing after three months follow-up may be underreported.

Motor, sensory, and visual deficits are seen preoperatively in patients who are candidates for hemispheric surgery. Worsening of contralateral hand function and hemianopia are expected adverse effects and not complications in patients with preserved function. On the other hand, improved motor function is possible in children because of functional reorganization.[209]

Hamartoma procedures

A hypothalamic hamartoma is a disorder of neuronal development which causes drug-resistant epilepsy, typically involving gelastic seizures. Several treatment modalities have been used including endoscopic surgery and minimally invasive procedures.[214] The cohort in Paper II comprised 15 hamartoma disconnections (11 in children), with a total of 1 major and 1 minor complication (6.7% each).

Disconnective procedures

The most common disconnective procedure is callosotomy, which most frequently involves complete or anterior two-third division of the corpus callosum. This procedure is based on the concept that the corpus callosum stands for most of the neuronal trafficking between the hemispheres and is an effective palliative treatment option for symptomatic generalized epilepsy, especially as regards traumatizing drop attacks.[215; 216]

In a systematic review of 12 case series comprising in total 377 pediatric callosotomy patients, one death was reported, and only one major complication (0.3% each).[19] Paper II reported 31 cases (24 in children) with one major (3.2%) and no minor complications. A transient disconnection syndrome including apathy, visual disturbances, and non-dominant neglect has been reported with various frequencies.[19; 216]

Multiple subpial transections is a rare procedure which aims to reduce propagation of seizure activity while preserving neurological function in a limited area near or in eloquent cortex.[217] Paper II reported 11 procedures with 1 minor complication.

Minimally invasive procedures

In recent years, several invasive procedures have been introduced where different methods are used to ablate the epileptogenic zone in situ. A review of these modalities is of interest because they are thought to have a favorable adverse effect profile due to the avoidance of open surgery.

None of these procedures were addressed in Paper II as they were not performed in Sweden during the studied time period. In Paper IV, minimally invasive procedures are not listed in the protocol but can be reported as “other procedures.”

Laser interstitial thermal therapy

In MRI-guided laser interstitial thermal therapy (LITT), laser light is used to thermally ablate a limited target reached by a stereotactically placed optical fiber. It is most commonly used for mesial temporal lobe epilepsy. Further indications include brain tumors, cavernomas, hypothalamic hamartomas, and radiation necrosis.[218; 219]

Complications may arise from catheter placement, hyperthermia, or the cooling systems that are used during the procedure.[218] Reviews of this method report adverse events of any duration in 16-24%, not differentiating between expected adverse events and complications.[219; 220] Permanent neurological symptoms are seen in about 6% of the cases.[218]

Radiofrequency thermocoagulation

During SEEG, the diagnostic electrodes can be used to create lesions in the epileptogenic zone using radiofrequency thermocoagulation (RFTC). RFTC is mostly used as a palliative treatment for cases where resective surgery is not feasible.[221]

In a systematic review and meta-analysis, the pooled prevalence for permanent neurological symptoms was 2.5% (95% confidence interval [CI] 1.2-5.3%). No other adverse outcomes were reported.[221] In the largest of the cohorts included in the meta-analysis and in a later publication on pediatric patients, neurological worsening was judged to be expected in half of the cases with permanent symptoms.[222; 223]

Stereotactic radiosurgery

Stereotactic radiosurgery for epilepsy (SRS) most often consists in a single-dose radiation delivered to the mesial temporal structures.[224; 225] In a multicenter RCT of this method, adverse events related to treatment occurred in 39% of the patients who had SRS and 11% of those who had TLR.[226] The seemingly high rate of adverse events with SRS is largely explained by symptoms of expected radiation edema developing some months after treatment. In visual field testing, about the same proportion of patients with SRS or ATL had postoperative quandrantanopia.[226]

Neurostimulation procedures

Several neurostimulation procedures are used for palliative treatment of drug-resistant epilepsy for patients who are not suitable surgical candidates, decline surgery, or continue to have seizures after surgery. These modalities are usually not included in epilepsy surgery series but will be mentioned here as they can sometimes be considered after surgical evaluations.[227]

Vagal nerve stimulation

With vagal nerve stimulation (VNS), a pacemaker-like generator implanted subcutaneously under the left clavicle delivers intermittent electrical stimulation through a lead connected to the left vagus nerve in the neck.[228]

Adverse effects of VNS are related to the implantation, to hardware failure, or to the stimulation itself. In observational series, complications related to implantation occurred in 8.6-12.0% per procedure.[229-232] Life-threatening peritracheal hemorrhage has occurred in rare cases.[229] Hardware complications have been reported in 3.7-9.5%.[229; 230; 232; 233] Stimulation-related adverse effect often improve by time or changed stimulation parameters.[234; 235]

Direct brain stimulation

Deep brain stimulation (DBS) of the anterior thalamic nucleus is approved in Europe as adjunctive treatment of drug-resistant epilepsy due to efficacy in short-term RCT, but the true effect size is unknown.[235-237] In a systematic review of DBS various indications, infectious complications were found in 5.1%, lead migration in 1.6%, and lead fracture in 1.5% of implantations.[238]

With responsive neurostimulation (RNS), electrical stimulation is triggered by epileptogenic activity detected by continuous intracranial EEG recording of a limited cortical area. The method is recommended by some centers when resection of a limited epileptogenic zone is not feasible because it is overlapping eloquent cortex.[224] Although approved in the USA, RNS is still an experimental treatment modality, and data on its adverse effects are scarce.[235; 237]

Risk factors

As for invasive diagnostic procedures, risk factors for adverse effects of epilepsy surgery are important to identify the patients who are most likely to benefit from the procedure and, if possible, reduce the rate of complications.

Age

Several studies have shown that older patients who undergo epilepsy surgery have similar seizure outcomes compared to younger patients.[239-247] However, there are concerns that older patients may have a higher risk for complications, due to an increasing prevalence of somatic comorbidities, brain atrophy, increasing tissue fragility, or unknown factors.[248]

In Paper II, we found an increased risk for complications (major or minor) with higher age (odds ratio 1.26 per increasing 10-year interval, 95% CI 1.09-1.45). On the other hand, there was no significant association between major complications and higher age. In categorical analysis, there was a significant association between complications and age when patients 35 years or older were compared to patients under 35 years (OR 2.23, 95% CI 1.43-3.46), but not when adults were compared to children.

Several reports have found a higher risk for complications in older compared to younger patients,[131; 147; 239; 240; 247; 249; 250] while other studies report no difference.[187; 243; 244; 251] Further publications report low rates of complications for older patients although lacking a younger control group.[242; 245] Most studies are retrospective and include small numbers of patients in the older group. Age is most often analyzed in categorical comparisons with a cut-off ranging from 12-60 years.[251; 252]

One possibility is that an increased risk of complications in the elderly is driven by increasing comorbidities.[248] We could not analyze this question in Paper II because SNESUR does not contain comorbidity data. One register-based study based on the National Inpatient Sample (NIS) found a correlation between increasing comorbidity index and an increasing incidence of complications. Higher age was a significant predictor for complications although it appears that comorbidity was not included in the multivariable analysis in this study.[253]

Three studies using data from the NSQIP database included age and different markers for comorbidity in multivariable models. One report found that higher age was an independent predictor for discharge disposition other than home despite controlling for several comorbidity variables including ASA (American Society of Anesthesiologists) status.[176] A second study reported that although higher age was related to complications in univariable analysis, only chronic steroid use and prior stroke (interpreted as markers for comorbidity) were independent predictors in multivariable analysis.[175] The third study reported that both age and ASA status were independent predictors for complications.[177]

Some single center studies have presented comorbidity data although not related in multivariable analysis to complications.[242; 244] One study reported similar complication rates for patients above and under 60 years despite a higher mean comorbidity index in the older group.[252]

Although the majority of studies indicate a higher risk with increasing age, it may be that complications are more common in specific age groups, for instance for children during the first years of life.[254; 255] One study comprising only pediatric patients surprisingly found that complications were significantly related to lower age at surgery.[135] In Paper II we found no difference in the rate of complications in patients under compared to above three years of age, although there were few patients in the younger group.

It should be noted that although many studies find a higher risk for complications in older patients, the risk increase appears modest, as indicated by the odds ratio reported in Paper II. Indeed, there were no major complications in the older group in this cohort, similar to the previous Swedish study.[249] Risk increase with higher age can to some extent be underestimated because of selection bias, i.e., that elderly patients are likely to have surgery only if they are judged to have a low risk for their age. Still, older age should in general not be considered as a contraindication to surgery.

Finally, it should be mentioned that other factors than surgical risk may be decisive when epilepsy surgery is considered for elderly patients, such as social factors and an increased risk for cognitive worsening after TLR.[88; 243; 246]

Reoperations

Patient who have reoperations may have a higher risk of complications, for instance due to adherences. Two reviews of single center studies with 5-68 reoperations report heterogeneous results with complication rates ranging from 0-58% and a pooled prevalence of 13.5-20.6%.[256; 257]

The variation in complication rates depends to some extent on variations in the surgical panorama.[257] Varying or absent definitions of complications may also play a role. A high proportion of reported adverse events are VFD, which are frequently expected depending on the localization of the resection.[256] One study reported 58% complications, several of which were specified as neurological worsening after additional surgery near or overlapping eloquent cortex. This raises the question if these events are more to be considered as expected adverse events than complications.[258]

Classifying only unexpected events as complications, we reported in Paper II 3.8% major and 7.5% complications in 158 reoperations, similar to the rate for primary procedures.

Hospital volumes and surgical experience

One study reported a significantly lower risk for complications in hospitals with large surgical volumes (>15 procedures per year) compared to low-volume centers (<5 procedures per year).[259] Other studies have reported a decreased risk for complications with longer surgical experience,[167; 260] similar to in other neurosurgical procedures.[261]

In SNESUR, results are not compared between surgeons and centers. However, as shown in Paper II, epilepsy surgery is performed in six Swedish centers with a similar risk compared to larger international centers. Data on surgical experience and hospital volumes are difficult to compare across different educational and health care systems.

Other risk factors

Apart from age, no risk factors for complications have consistently been identified in the literature.[74] In Paper II, we found no significant association between complications (minor or major) or major complications and any of the potential predictors sex, reoperation, type of surgery, and previous invasive investigations. However, in Paper I, we reported that for patients who had a complication during the invasive investigation, the risk was increased for complications related to the subsequent epilepsy surgery procedure (OR 6.27, 95% CI 1.32-29.9). This association has not been reported in other studies, and the potential reasons are unknown.

Conclusions

Observational data provide rates for complications related to epilepsy surgery, but comparisons are often difficult due to heterogeneity in procedures, definitions, and study designs. Higher age is the most consistently indicated risk factor for complications and may be influenced by increasing comorbidities.

Epilepsy surgery failure

This chapter discusses seizure worsening, an understudied subgroup of epilepsy surgery failure with potentially high impact for the individual which we addressed in Paper III. Epilepsy surgery failure is not consistently defined in the literature but implies that the preoperative expectations in terms of seizure reduction are not met.

Classification of seizure outcome

There is no universal classification of seizure outcomes in epilepsy treatment studies. The primary endpoint of AED trials is usually the 50% responder rate, defined as the proportion of the patients who achieve an at least 50% reduction in the number of seizures during a certain period of time.[262] In epilepsy surgery studies, the Engel and ILAE classifications are the most widely used classifications of seizure outcome (Table 7).

The Engel classification grades seizure outcome from I (free from disabling seizures) to IV (no worthwhile improvement), with subclasses of each outcome class. The subclass Engel IA is often used and indicates complete absence of seizures since surgery, including freedom from aura.[263] The Engel classification in part depends on the terms “disabling” and “worthwhile” which leave room for subjectivity and are difficult to define.

The ILAE recommends quantitative grading of outcome as Class 1-6 based on the number of days with seizures counted on a year-by-year basis, except for the subclass 1 a, defined as complete seizure freedom since surgery.[264]

The classification used in SNESUR quantifies seizure outcome based on the change in average number of seizures per month over the last year before follow-up compared to the year before surgery (Table 7).[76]

Although the number of seizure days can be more reliable than the number of seizures,[264] the ILAE classification is less suitable for patients who have daily seizures, which is common among children with drug-resistant epilepsy.[18] Apart from the distinction between seizure freedom with or without aura, all the above outcome classifications are defined independently of the type and severity of seizures.[265] The Engel and ILAE classifications exclude the first postoperative weeks in the requirements for complete seizure freedom.

Table 7. Seizure outcome classifications for epilepsy surgery.

Engel classification[263]	I	Free from disabling seizures
	II	Rare disabling seizures
	III	Worthwhile improvement
	IV	No worthwhile improvement
ILAE classification[264]	1	Completely seizure-free without auras
	2	Only auras, no other seizures
	3	One to three seizure days per year, with or without aura
	4	Four seizure days per year to 50% reduction of baseline seizure days, with or without aura
	5	<50% reduction to >100% increase
	6	>100% increase
Classification in SNESUR[76]	1	Seizure-free (with or without aura)
	2	≥75% reduction in seizure frequency
	3	50-74% reduction in seizure frequency
	4	0-49% reduction in seizure frequency
	5	Worsening

Definitions of epilepsy surgery failure

Clavien et al. defined surgical failure as a subgroup of negative outcomes which implies that the procedure did not fulfil its original purpose, while not adding to the existing problem as is the case for complications and sequelae.[181] In epilepsy surgery, failure implies that the goal in terms of seizure reduction is not met, but the exact definition of this outcome varies.[266]

Many studies use the term failure synonymously with seizure recurrence, i.e., an outcome other than Engel I (or I A) or ILAE 1 (or 1-2).[256; 267-270] Other studies consider only the cases without significant improvement of seizures as failures. For instance, Penfield and Steeleman classified in the 1940s cases with less than 25% improvement as "failures" and outcomes with >50% improvement as "satisfactory".[271] More recent studies have grouped Engel I-II together as "good seizure outcome" and III-IV as "failure".[272; 273]

Indeed, the definition of failure would depend on preoperative expectations. First, patients may consider a less than complete reduction of seizures worthwhile.[53; 96] Second, some procedures are palliative in intention, for instance because the epileptogenic network is too extended to allow complete resection.[22] Finally, a limited resection near eloquent cortex which is followed by a more extensive re-operation due to seizure recurrence can be a planned surgical strategy to minimize the risk for neurological deficits.[258; 274]

Risk factors for seizure recurrence

Early postoperative seizures can arise from several reasons, most importantly failure to identify the epileptogenic zone in the presurgical evaluation or limited resection due to functional or technical constraints. Late recurrences are less well understood but may involve the development of an independent epileptogenic focus or network.[266; 275]

For both TLR and extratemporal resections, the presence of an identifiable lesion of MRI has been considered the most important predictor for seizure freedom.[62; 74; 276; 277] Interdependent of this finding, patients who need invasive investigations are less likely to become seizure-free.[62] However, more recent studies show that selected cohorts of patients with normal or inconclusive MRI can have similar outcomes compared to patients with clear MRI lesions.[74] Comparing seizure outcomes with different durations of epilepsy at the time of resective epilepsy surgery, the likelihood of seizure freedom is higher with earlier surgery regardless of the chosen cut-off for comparison.[278]

For TLR, positive predictive factors for seizure freedom include complete resection of the hippocampus, and pure temporal lobe epilepsy as opposed to temporal plus epilepsy (where the epileptogenic zone extends to neighboring cortical areas). Negative predictive factors include interictal EEG discharges contralateral to the resection, past history of trauma or infection, neuropsychological abnormalities, a high baseline seizure frequency, and previous TCS or status epilepticus.[74; 266; 269; 276; 279; 280]

Seizure recurrence is more common with extratemporal resections compared to TLR. Predictors for seizure freedom after extratemporal resections include complete resection of the suspected epileptogenic zone, focal interictal discharges on EEG, and pathology other than focal cortical dysplasia type I.[74; 266]

Seizure worsening

The Engel classification has a subclass IV C "seizures worse", where the quantitative or qualitative meaning of "worse" is not further defined.[281] In the ILAE classification, "worsening" (Class 6) is defined as >100% increase of baseline seizure days, where the last year before follow-up is compared to the year before surgery.[264] In SNESUR, "worsening" indicates an increase in the average monthly total of seizures the year preceding surgery or follow-up.[76]

Despite these classifications, few studies report worsening separately. Outcomes are often classified in larger groups. Of the three RCT for epilepsy surgery, the TLR trial by Wiebe et al. did not specify the rate of seizure increase,[16] whereas the study by Engel et al., using the ILAE classification, reported 0/15 worsening in the patients who had surgery, compared to 3/23 (13%) in the medical group.[17] Dwivedi et al. reported in their RCT of different surgical procedures for children with drug-resistant epilepsy that none of the patients in the surgery group had ILAE class 6 at one year after surgery, in contrast to 58% in the medical therapy group.[18]

Increased seizure frequency

To our knowledge, there is only one previous publication dedicated specifically to seizure worsening. In this retrospective single-center cohort of patients who underwent unilobar resections, Sarkis et al. found an at least double increase in the average monthly seizure frequency in 9.8% of those who had at least one seizure after surgery.[78]

In Paper III, we used the prospective SNESUR register to find patients who underwent any type of epilepsy surgery in Sweden 1990-2015 and had at least two years of follow-up. Of 1407 cases with follow-up, 4.0% had increased seizure frequency. This outcome was defined as an increase in the average number of seizures per month the second year after surgery compared to the year preceding surgery. In a post-hoc analysis, we computed the number of patients with >100% increase in the number of seizures, which was seen in 2.8% of the cases. Of those who were not seizure-free, 6.8% had increased and 4.8% doubled seizure frequency. Thus, the rate of increased seizure frequency is similar in the two studies, although there are differences in the patient selection and definitions of outcomes as described above.

New-onset tonic-clonic seizures

An important form of seizure worsening regards the emergence of more severe seizure types with a higher potential for injuries. Sarkis et al. reported that 1.4% of the patients with seizure recurrence had new-onset TCS, and 8.0% had increased number of TCS.

In Paper III, 3.9% of the cohort had new-onset TCS after epilepsy surgery, or 6.6% of those who did not have TCS preoperatively. This is higher than in the previous study, which is probably explained by the inclusion of non-resective procedures, which had an increased risk for TCS in this data set.

Other forms of seizure worsening

Other forms of seizure worsening have been reported in case studies or small series, including new-onset status epilepticus,[78] loss of aura which may lead to a higher risk of injuries,[282] and changed diurnal patterns with more unpredictable or disturbing seizures.[281] We were not able to determine the rate of these outcomes as they are not recorded in SNESUR. Sarkis et al. reported new-onset status epilepticus in 2.2% in their cohort of patients with seizure recurrence.[78]

Risk factors for seizure worsening

In the study by Sarkis et al., a higher risk for increased seizures was seen in extratemporal resections compared to TLR, and in patients with low preoperative seizure frequency compared to patients with high preoperative seizure frequency.[78] Cases with new-onset TCS were too few to explore risk factors, but incomplete resection and multiple recorded ictal patterns were identified as risk factors for increased number of TCS.[78]

In Paper III, we found a higher risk for both increased seizure frequency and new-onset TCS in reoperations compared to first surgery. Predictors for each outcome were explored for first surgeries. Lower age at surgery and procedures other than TLR independently predicted increase in multivariable analysis. Regarding new-onset TCS, the presence of a preoperative neurological deficit was the only significant predictor in multivariable analysis. Predictors significant only in univariable analysis included intellectual disability and, for increased seizure frequency, high preoperative seizure frequency.

The risk factor analyses in these studies are exploratory due to the small numbers of patients with each outcome. The association between lower age at surgery and seizure increase was seen only for extratemporal procedures in our study. Children with extratemporal epilepsies often have malformations of cortical development, which may involve more extended epileptogenic networks.[191; 277] Reoperations, extratemporal procedures, incomplete resection, multiple seizure patterns, intellectual disability, and high preoperative seizure frequency – which were associated with seizure worsening – have also been identified as predictors for seizure recurrence in different studies, as mentioned previously.

As seen, many risk factors are the same for seizure recurrence and seizure worsening. We hypothesize that these predictors are markers for more extended epileptogenic networks, which might be more prone to seizure initiation and propagation following incomplete resection.[283-287] To elucidate this hypothesis, future work is needed where preoperative neurophysiologic brain connectivity and postoperative histopathology are analyzed in relation to seizure recurrence and worsening.

Limitations in studies of seizure worsening

In Paper III, follow-up was available for 89% of the procedures performed during the inclusion period. In some cases, follow-up was not performed because the patient had a reoperation within two years, which would somewhat underestimate the rates of worsening if some patients had another surgery because of seizure worsening.

A general limitation for studies of seizure worsening is that without controls, causality cannot be inferred from surgical procedures to seizure worsening. Short-term fluctuations in seizure frequency are common in drug-resistant epilepsy, but the influence of this factor is minimized because seizures are reported as an average over a year.[262] New-onset TCS can occur after reducing AED therapy.[288] This is a possible explanation for worsening in individual cases, although no patient with seizure increase or new-onset TCS in our study was completely off medication at follow-up.

Long-term follow-up after epilepsy surgery shows mixed trajectories, with recurrent seizures in a minority of patients who were initially seizure-free, improved seizure control in a proportion of those who have seizures after surgery, and fluctuating patterns of recurrence and remission in some patients.[75; 289; 290] For some patients, worsening of seizures could be due to progression of an underlying disorder.[281] Long-term follow-up of patients who have seizure worsening at the first postoperative follow-up could be informative to investigate if this outcome is stable over time.

Conclusions

Seizure worsening after epilepsy surgery is rare and methodologically challenging to distinguish from the natural course of drug-resistant epilepsy. Controlled studies where surgical cases are compared to cases without surgery are difficult to perform, but studies on the long-term trajectories for patients who have seizure worsening after surgery can also be informative. Lower age at surgery, procedures other than TLR, and preoperative neurological deficits are potential predictors for seizure worsening. Similar risk factors have been reported for seizure recurrence and may be markers for more extended epileptogenic networks.

Prevention of adverse events

Data on adverse events are necessary for surgical quality assessments, where rates of complications allow comparisons between different centers, procedures, and surgical routines, and may prompt improvements in procedures where relevant.

General measures to prevent complications

Although complications are, by definition, unexpected adverse events, preventive measures can reduce the likelihood for adverse outcomes. General neurosurgical routines based on controlled studies or surgical experience involve careful patient selection, review of potential intraoperative risks, correct positioning, and interventions for reducing thromboembolic complications and edema.[291] Data from imaging and neuropsychological investigations are used to inform surgical strategies and assess the risk for neurological worsening.[24; 48] When complications do occur, critical analysis of individual cases will encourage improvements of surgical standards.[59; 292; 293]

Secular trends

In many epilepsy surgery studies, patients are included over a very long time period, which may obscure changes in complication rates due to changing patient selection, surgical techniques, or postoperative management. Secular trends have been analyzed in a few studies.

Tebo et al. conducted a systematic review of previous publications to compare the rate of complications for procedures performed 1980-1995 and 1996-2012.[294] In TLR (including SAH), neurological deficits decreased from 41.8% to 5.2% and persistent neurological deficits from 9.7% to 0.8%. In extratemporal and multilobar resections, neurological deficits decreased from 30.2% to 19.5%, and persistent deficits from 9.0% to 3.2%. Finally, in invasive electrode procedures, persistent deficits were very rare in both time periods, while infections increased from 2.3% to 4.3% and hematomas from 1.9% to 4.2%.

The marked decrease in complications may indicate improvements in imaging or surgical techniques.[294] However, the rate of postoperative neurological deficits in the earlier cohort is surprisingly high for TLR both compared to other procedures in the same study and rates reported for TLR in other studies. For instance, there were 9.3% minor and 2.8% major complications (including persistent deficits) reported for TLR in Sweden 1990-1995.[131] Although the authors acknowledge discrepancies in methodology and completeness in the underlying studies, complications were not defined for the data extraction. It may therefore be the case that complications have been defined differently in the two cohorts, for instance if more strict criteria for visual field complications were used in later studies.

Other investigations of secular trends have mixed tendencies. One study reported a significant decrease in the rate of complications in pediatric epilepsy surgery 1986-1997 compared to 1998-2008, but definitions and methods of follow-up were not specified.[295] In contrast, two single center studies on pediatric epilepsy surgery and one retrospective multicenter review of epilepsy surgery in Europe using strict definitions of complications reported stable rates over time.[35; 36; 296] In SNESUR, there were numerically lower complication rates 1996-2010 (Paper II) compared to 1990-1995,[131] but the differences were not statistically significant.

Preventing infections

Surgical site infections occur in all fields of surgery and are associated with increased hospital stay and mortality.[297] The risk of infections increases with age and comorbidities as well as the duration and complexity of surgery.[298] Neurosurgical infections range from superficial wound infections to deep infections such as bone flap osteomyelitis, subdural empyema, and brain abscess.[299] In Paper I, infections were reported in 0.7% of intracranial EEG registrations, and the 2.2% rate reported for epilepsy surgery procedures in Paper II was comparable to the overall risk in elective neurosurgery.

Postoperative infections are considered as an important measure of surgical quality. Detailed guidelines for pre- and intraoperative routines have been provided.[297; 300; 301] Preoperative antibiotics reduce the risk of postoperative infections and belong to the standard of care in major surgery. In contrast, prolonged use of antibiotics during the postoperative period increases costs and promotes microbial resistance without proven additional value.[297; 299-301]. In neurosurgery, postoperative antibiotics are often administered outside the recommendations in general guidelines.[302]

Infections in epilepsy surgery

There are few RCT of antibiotics for specific neurosurgical procedures. During invasive EEG monitoring, the risk of infection is potentially increased due to the presence of a foreign body or persistent CSF leakage. Some centers routinely administer prophylactic antibiotics during the entire registration period.[117] Other centers administer antibiotics during a limited number of days,[129] as a single preoperative dose,[148] or only if an infection is suspected.[138; 145]

A non-randomized study compared three antibiotic regimens in consecutive groups of patients who underwent monitoring with subdural strip electrodes.[303] The same rate of infections was found in a first group who received an intravenous loading dose of an antibiotic followed by two daily doses during the entire registration period, and in a second group who had a single dose the morning before implantation. Infections were more common in a third group without antibiotic prophylaxis, although the difference was not statistically significant.[303] Another study found no significant change in the rate of infections after introducing antibiotic prophylaxis during the course of subdural registrations.[251] Some centers have reported low rates of infection without the administration of any systemic prophylaxis, but these results are difficult to interpret because there were no controls.[147]

In summary, the optimal regimen for prophylaxis in invasive monitoring remains to be determined. Indirect meta-analyses of existing studies are difficult to perform because many uncontrolled observational studies do not specify antibiotic regimens. Because of this, we proposed prophylactic antibiotics as one of the items to report in a protocol for complications in invasive investigations and epilepsy surgery (Paper IV).

Preventing neurologic deficits

Regarding neurologic deficits, the general challenge in epilepsy surgery is to remove the necessary amount of tissue to achieve seizure freedom while at the same time minimizing damage to parts of the brain that are not involved in the epileptogenic network. A less extensive resection may lead to a lower risk for postoperative deficits, while an incomplete resection of the epileptogenic zone carries a higher risk of seizure recurrence.

The optimal extent of a resection is judged on an individual basis which makes it difficult to conduct comparative studies of different surgical procedures. As described previously, comparisons between ATL and SAH are inconclusive, while complications in hemispheric procedures have been reduced with modified surgical strategies. In some cases, expected neurological worsening is a part of the complex trade-off when considering surgery near eloquent cortex, and there is no consensus about what chances of seizure freedom are acceptable for justifying a new deficit.[274; 304]

Pre- and intraoperative surgical planning

VFD occur in a large proportion of patients who have TLR and are usually not considered as complications. However, minor VFD may have practical implications for the patient even in the absence of subjective symptoms. Studies indicate that 20-50% of patients who have TLR have a VFD that fails to fulfil criteria in driving legislation, which will preclude driving even if the patient becomes seizure-free.[190; 305-307] An important goal is therefore to reduce the incidence of VFD if possible without jeopardizing seizure outcomes.

It has been known for a long time that the risk of a VFD after TLR depends on the size of the resection,[1] which has been confirmed in later studies using formal visual field testing.[308] However, the extent of VFD is not completely predicted by resection size due to individual variations in the anatomy of the visual pathways.[305]

Diffusion tensor imaging (DTI) tractography is an MRI processing technique which is used to visualize white matter tracts including the visual pathways. Several studies have demonstrated a precise correlation between damage to the optic radiation as indicated by tractography and the extent of postoperative VFD.[305; 309] One small study showed that tractography reduced the risk for postoperative VFD in patients who had TLR guided by intraoperative MRI. None of the patients who had tractography had a VFD that precluded driving. Seizure outcomes were similar in both groups.[310] These findings have to be replicated in further studies, preferably RCT.

Neuronavigation has increased anatomical precision by allowing real-time imaging of parts of the brain that are not under direct visual contact during surgery.[311] In a retrospective study, fewer neurological deficits were seen with neuronavigation compared to conventional neurosurgery,[312] but a systematic review did not find compelling evidence for this.[313] Intraoperative functional mapping is useful to reduce the risk of postoperative deficits after surgery near eloquent cortex.[26]

Conclusions

Data on adverse effects may serve as a benchmark to compare results in different centers and for different surgical procedures. Prospective multicenter studies are needed to investigate risk factors for surgical complications and compare preventive strategies. New methods for preoperative planning may improve neurological outcomes.

Methodological issues in studies of adverse events

Well-designed observational studies are needed to analyze adverse effects of epilepsy surgery and invasive procedures. This chapter will discuss methodological issues in the existing literature and specifically a protocol for prospective reporting of complications which we proposed in Paper IV.

Study design

In general, an RCT is considered the best study design for evidence-based medicine, as it controls for known and unknown confounders. However, the number of included patients in a surgical RCT is typically small, which makes it less suitable for studying rare outcomes such as complications and, for epilepsy surgery, seizure worsening. There are three RCT comparing epilepsy surgery and medical therapy and a limited number of RCT comparing different surgical procedures. None of these had surgical or neurological complications or seizure worsening as their primary endpoint and data on these outcomes are frequently incomplete.[16-18; 62]

Analyzing complications and seizure worsening is therefore dependent on well-designed observational studies. For seizure worsening, the inclusion of a control group would be ideal to distinguish the effects of surgery from the natural course of the disease.[78; 314] As for complications, controls are only occasionally relevant as the events in question are inherently related to a surgical procedure. One controlled study extracted data on adverse events during elective admissions among patients with drug-resistant focal epilepsy from a national database.[315] An expected finding was that intracranial hemorrhage and status epilepticus was more common among patients who were admitted for surgery or invasive procedures compared to patients who were admitted for other reasons. Potentially more interesting, surgical and non-surgical patients had the same rate of thrombosis, sepsis, and hydrocephalus, but underreporting is likely as there were no reported cases of hemiparesis or infection in almost 500 surgically treated patients.[315]

Most publications on surgical and neurological complications are single-center studies, some of them reporting cases operated on by a single surgeon.[147; 170; 260] This study design facilitates comparisons within the cohort, because patient selection, surgical protocols, and reporting are likely to be more consistent compared to in multicenter studies.[170] However, multicenter studies allow for better generalizability. SNESUR is a national database comprising all procedures performed in the six operating center in Sweden. Because of this, studies based on SNESUR are also population-based, which adds to the generalizability of the results.

Data collection

The majority of studies on outcomes of epilepsy surgery have a retrospective study design.[62] Data on adverse effects are most frequently based on medical chart review, which relies of the completeness of the records for the outcome of interest. A prospective study design identifies factors of interest to report before follow-up, which facilitates complete and reproducible reporting.[314]

Register-based studies allow the combination of multicenter inclusion and prospective data collection but have limitations in the number of included variables. Therefore, detailed post hoc analyses of potential confounding variables are not always feasible.

Prospective datasets are the Nationwide Inpatient Sample (NIS)[213; 253; 315; 316] and the Kid's Inpatient Database (KID).[317] While these databases provide national samples of the rate of complications, they are administrative and not clinical database, and the codes used to identify cases are not always specific enough to differentiate surgical procedures.[175; 318]

A number of epilepsy surgery studies use NSQIP, which was instituted by the American College of Surgeons as a means to monitor adverse effects from surgical procedures.[175; 176; 319; 320] In this protocol, a list of complications is prospectively evaluated and reported within 30 days after the procedure.[175] Although NSQIP is a database for surgical adverse events, it is not designed specifically for epilepsy surgery, and potentially important data on surgical approach and technique are lacking.[175]

The rate of complications also depends on the method for their detection. Concerning VFD, Georgiadis et al. reported in their review of TLR rates ranging from 0-69% in the underlying studies. Many reports do not specify the method for visual field assessment, while others rely on formal perimetry.[64] Bedside VFD testing and subjective symptoms are not reliable to predict even major VFD that would preclude driving.[307] The studies reporting no deficits did not systematically assess these outcomes, whereas the study with the highest rate performed a thorough ophthalmological examination in all subjects.[321] In general, studies focusing on a specific adverse event typically present higher rates for the relevant outcome.[134; 144; 321]

Although most surgical complications present early after surgery, the detection of complications depends in some cases on the time point for evaluation. A VFD may improve after the immediate postsurgical period.[322] Many studies assess complications during the admission for surgery or within 30 days,[175] which may be insufficient to detect bone flap infections and hydrocephalus.

In SNESUR, complications are confirmed or denied at the time of the first postoperative follow-up three months after surgery (Papers I-II). Complications are specified in free text instead of monitored per complication. Seizure types and seizure frequencies are reported at the time of the preoperative evaluation and at predetermined time points for follow-up, the first one two years after surgery (Paper III), and then subsequently at five, ten, 15, and 20 years after surgery.[76]

Definitions

Clear definitions of outcomes are critical in all clinical studies.[60; 61; 323; 324] Inconsistent reporting of adverse effects has been highlighted in several reviews of epilepsy surgery and invasive procedures. A review of surgical RCT in general surgery found that intraoperative complications were defined in only 13% and postoperative complications in 50% of the studies, independent of whether assessment of complications was the primary objective of the study or not.[185]

Definitions of complications

There is no universally accepted definition of a neurosurgical complication.[59; 325-327] In epilepsy surgery, it is especially important to distinguish unexpected complications from expected worsening which is often a part of the trade-off when weighing the chances of seizure freedom against the risk of adverse effects. Many studies of complications in epilepsy surgery and invasive procedures do not contain a definition of complications, which is emphasized in several reviews as it obscures the interpretation of outcome data.[62-65]

Clavien et al. defined complications as any deviation from the normal postoperative course, while sequelae were understood as problems inherent to the procedure, i.e., "an accepted alteration in structure or function of the body that is embodied in the procedure."[181] Other authors have more inclusively defined a complication as "every unwanted development of the illness of the patient or of the treatment of the patient's illness that occurs in the clinic."[328]

Similar to the definition of Clavien et al., several epilepsy surgery studies, including Papers I-II, have defined a complication as an unwanted, unexpected, and uncommon event after a diagnostic or therapeutic procedure.[131; 168] Other studies have included all adverse events which occur within a certain time after surgery or invasive investigations,[121; 329] at least if it is related to the procedure.[330]

If distinguished from complications, expected adverse events are considered to be very common, preoperatively discussed with, and accepted by the patient. Common examples are upper quadrantanopia after TLR, worsening of intact hand function after hemispherotomy, and minor CSF leakage in subdural grid evaluations.[131; 147; 167]

Classification

In Paper IV, we reviewed classification of complications. Many studies classify complications as surgical and medical; surgical, neurological, and medical; or surgical and neurological complications.[65] In contrast to varying severity grading systems, such differences seldom pose a major problem for comparisons between studies, except in that it is not always clear if complications are counted per individual or per category.

Grading of complications

One of the most widely used system for classifying surgical complications is the Clavien-Dindo classification (1992, revised 2004). Here, complications are graded hierarchically based on the invasiveness of the measures needed to reverse the complication (bedside intervention, surgical interventions, intensive care, etc.) and the impact of the complication (organ failure, death). A suffix can be added to indicate that the patient still suffers from disability at the time of discharge [181; 331; 332]. The similar Accordion system of 2009 is more strictly focused on necessary interventions.[333]

Neither of these systems have been used in epilepsy surgery, but a similar classification devised for general surgery by Landriel Ibañes et al.[334] has recently been used for TLR.[173]

As reviewed in Paper IV, several systems have been used for grading of complications related to epilepsy surgery and invasive procedures. In agreement with the above mentioned classifications, several studies have graded complications depending on changed medical management or additional surgery.[162] Other included parameters are prolongation of hospital stay and whether Glasgow Coma Scale was affected.[335; 336] Several studies classify complications as major vs. minor, or permanent vs. transient, depending on the duration of symptoms.[131; 147; 167; 337] The duration for defining permanent symptoms ranges from 3-12 months.[131; 167] One study classified as major complications any new unexpected deficits whether permanent or not.[135] Other systems suggest classification based on the type of resulting neurological symptoms.[338] Some classifications have chosen different combinations of the aforementioned items.[137; 145; 169; 339; 340]

A recent practice parameter proposed a grading system for expected neurological adverse effects based on how critical various functions were considered according to participants in a survey among surgical teams. A permanent language or dominant hand motor deficit was considered worse than a transient deficit or, for instance, a somatosensory deficit or a reduction in executive function.[274] However, the given examples are not exhaustive and remain somewhat arbitrary as patient perspectives have not been investigated.

Some authors have argued that complications should not be classified based on their outcome but on their causes, e.g., if they are predictable and/or avoidable.[59;

[341] Gozal et al. classified complications in neurosurgery based on the cause of the complication as determined on a collegial conference as related to indication errors, procedural errors, technical errors, judgement errors, and critical events.[59]

Statistical methods

In most investigations of risk factors for adverse outcomes, control for confounding variables was not initially planned in the study design. Therefore, such studies need statistical methods for multivariable analysis that are adequate for rare outcomes.[314] In Paper III, risk factors were analyzed in stepwise multivariable logistic regression, which is a predictive analysis for binary outcomes.[342]

A proposal for improved reporting of complications

In Paper IV, we aimed to address some of the methodological issues encountered in complication studies though proposing and evaluating a protocol for the reporting of complications. First, we aimed to include potentially relevant background factors which are often lacking in publications, such as the number of electrodes in invasive investigations and specification of antibiotic regimens. Second, we decided not to endorse any existing severity scale but instead to incorporate relevant aspects of previous classifications in a "multidimensional" classification scheme. Third, we aimed to add consequences of complications on ADL, which has not so far been implemented in existing classifications and in one study was found to be poorly correlated to therapy-oriented grading of severity.[343] We therefore proposed a detailed characterization of the procedure and reporting of complications in terms of immediate consequences, permanent symptoms, and consequences on ADL and dependency (Table 8).

Development and characteristics of the protocol

The basis for the protocol was a review of previous definitions and classifications as summarized in the last section. A first version of the protocol was drafted within the Epilepsy Research Group at the Sahlgrenska Academy, University of Gothenburg. This protocol was discussed and revised within an international network of epilepsy centers, E-pilepsy, and after further revision endorsed by the ILAE Commission on Surgical Therapies and the ILAE Task Force on Pediatric Epilepsy Surgery.

For the purposes of the protocol, complications are defined as unwanted, unexpected, and uncommon events directly related to an invasive diagnostic procedure, surgical resection, or disconnection. For ADL function, we decided to use the modified Rankin Scale (mRS) because it has been validated in several neurological and neurosurgical conditions.[344]

Table 8. Items reported in a proposed protocol for complications in invasive investigations and epilepsy surgery (Paper IV).

1	Operating center, number, and basic patient characteristics such as age, sex, and preoperative deficits.
2	Detailed characterization of the procedures: for invasive investigations including type, number, and laterality of electrodes, and the duration of monitoring; for epilepsy surgery the type and localization of the procedure.
3	Specification of any preoperative antibiotics and/or medical venous thromboembolism prophylaxis.
4	Specification of one or several complications in a multiple-choice fashion. If no complication occurs, the relevant box is ticked and the reporting procedures stops here.
5	Specification of any new and unexpected neurological deficits or unexpected worsening of deficits during the postoperative period.
6	Characterization of the impact of complications in terms of unplanned surgical procedures, readmission or prolonged hospital stay, and if they are life-threatening or result in death.
7	Description of permanent neurological symptoms as noted during the postoperative period which persist six months after surgery.
8	Reporting of the consequences of permanent symptoms on activities of daily living and dependency according to the modified Rankin scale.

Evaluation of the protocol

The final protocol was evaluated in three of the centers that participated in the development of the protocol, in Gothenburg, Lyon, and London. It was used for SEEG investigations and a range of epilepsy surgery procedures in patients of various ages, some of whom had complications.

Reporting was almost complete with the following exceptions. First, the number of electrode contacts was not easily retrieved for SEEG implantations. We included this item based on previous studies correlating the number of electrode contacts in SDE to complications. However, the same correlation has not been reported for SEEG and is theoretically less likely. Therefore, we will exclude this item for SEEG implantations in future revisions of the protocol.

Second, we noted some inconsistencies regarding the reporting of mRS. The mRS is not in its original form designed for pediatric studies in that some classes are defined based on the need for assistance in ADL, which naturally varies depending on the child's age.[345] Moreover, it is not suited for cases with significant premorbid disability, because some mRS classes are defined in terms of ability to carry out previous activities.[346] It could even be argued that mRS 0 or "no symptoms at all" would not be appropriate if the patient has no complication but continues to have seizures.

It should finally be acknowledged that the proposed protocol does not address cognitive or psychiatric adverse effects, which need to documented and analyzed separately. Patient-reported aspects including measures of health-related quality of life have not been addressed in previous studies of complications and will have to be investigated in future research before inclusion in a protocol.

Conclusions

Well-designed observational studies are necessary for studying rare outcomes. Standardized protocols for reporting complications will facilitate multicenter studies and meta-analyses, which are often needed to accrue the numbers of cases required for risk factor analysis. The impact of complications on ADL and quality of life remains to be studied.

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Conclusions

Information on adverse effects from epilepsy surgery is an essential part of counseling of patients and families, where the benefits of surgery and the risks of continuing seizures are equally considered.

Invasive diagnostic procedures carry a risk for serious adverse events, but the risk for subsequent permanent symptoms is low. Invasive electrode procedures must be planned individually to balance the maximum diagnostic yield against an increased risk with more extensive implantations.

In epilepsy surgery, the risk of mortality is very low. As for any neurosurgical procedure, complications do occur which must be addressed in counseling. The rate of neurologic symptoms after epilepsy surgery depends highly on definitions of outcomes and the relation of a resection to eloquent cortex. If only unexpected symptoms are counted as complications, less than one in twenty will have neurologic worsening which persists beyond several months. Higher age at surgery and comorbidities may increase the risk of complications.

Worsening of seizures is rare after epilepsy surgery, especially considering the much higher rate of significant reduction of seizures, including freedom from tonic-clonic seizures in many patients who have such before surgery. Risk factors for seizure worsening may inform decision making before surgery after replication in further studies.

Prevention of adverse effects depends on multiple factors. Multicenter studies are needed to analyze risk factors for complications and clarify optimal perioperative management including the best measures to reduce infections. Improved methods for preoperative planning may reduce the risk for postoperative neurological deficits.

Due to the limitations in patient recruitment and follow-up in randomized controlled trials, adverse effects of epilepsy surgery must be documented in well-designed observational studies. Clear definitions of outcomes, prospective data collection, and multicenter inclusion are some of the factors which help to ensure scientific quality and will allow future meta-analyses.

Acknowledgement

I would like to express my sincere gratitude to all who have contributed to the realization of this thesis. In particular, I would like to thank the following:

Professor Kristina Malmgren, my supervisor, who introduced me clinically and scientifically to epilepsy surgery, and suggested that the downsides of what we do would be a suitable project for someone with a philosophical and slightly pessimistic inclination. Thank you for sharing your enthusiasm for improving epilepsy care, your knowledge, feedback, encouragement, and writing skills.

Professor Bertil Rydenhag, my co-supervisor, for sharing your expertise in epilepsy surgery, your ethical perspective on neurosurgery, and for providing encouragement and constructive criticism.

All patients who shared their clinical data and made possible the Swedish National Epilepsy Surgery Register (SNESUR).

Roland Flink, former register manager for SNESUR, for your contributions to the register and for co-authoring Papers I-II.

Anna Edelvik Tranberg, register manager for SNESUR and co-author of Papers I and III, for support and encouragement throughout my PhD studies.

Our international collaborators, including co-authors J. Helen Cross, Sylvain Rheims, Philippe Ryvlin, and Michael R. Sperling, for your contributions to Paper IV. I would also like to thank Christoph Helmstaedter for helpful discussion on cognitive adverse effects.

Our colleagues in the epilepsy surgery teams in Linköping, Lund, Stockholm, Umeå, and Uppsala, the steering committee for SNESUR, and its register administrator, Judith Klecki.

Mattias Molin, Nils-Gunnar Pehrsson, and Aldina Pivodic at Statistiska Konsultgruppen for valuable statistical assistance.

Ingrid "Bobo" Olsson and Johan Zelano for proofreading and helpful suggestions.

My colleagues and friends Anna Edelvik Tranberg and Johan Zelano for insightful discussions about neurology, epilepsy, research, and much else, and for helping me to cope with the adverse effects of PhD studies.

Epilepsy surgery coordinator Christina Charling and former epilepsy surgery coordinator Gerd Ekstedt, for keeping track of everything.

My co-workers within the epilepsy surgery team in Gothenburg, including Louise Carstam, Anna Edelvik Tranberg, Anders Hedström, David Krýsl, Sofia Ljunggren, Kristina Malmgren, Daniel Nilsson, Josefin Nilsson, and Bertil Rydenhag, for stimulating and instructive discussions.

My co-workers within the epilepsy team and our colleagues at the Queen Silvia Children's Hospital, Sahlgrenska University Hospital, Gothenburg.

All colleagues in the department of neurology at the Sahlgrenska University Hospital.

The Sahlgrenska University Hospital and the Sahlgrenska Academy for providing the facilities for clinical research including the ALF PhD fellowship.

Former teachers and fellow students at the departments of philosophy and religious sciences of the Universities of Gothenburg, Lund, Umeå, and Uppsala, for training in critical thinking.

A very special thanks to my wonderful family, Jenny, Gustaf, and Folke, for love, patience, and inspiration. Thanks to our families for always helping us, and to our friends for encouragement and support.

This work was supported by grants from the Swedish state under the agreement between the Swedish government and the county councils, the ALF-agreement (grant ALFGBG-517901), and the Margarethahemmet foundation. The author has also received travel grants for congress presentations from the Gothenburg Foundation for Neurological Research and the Gothenburg Medical Society.

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