Paediatric Epilepsy Surgery in a Middle-income country: The Red Cross War Memorial Children's Hospital experience

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Declaration: Statement of originality

I, Lizet Louw, completed the work contained in this dissertation at the University of Cape Town between March 2020 and June 2022. It is original work except for where due reference has been made. It has not, nor will it be, submitted for the award at any other University.

Signature: Signed by candidate

Date: 14/09/22

Certification

The undersigned certifies that he has read and hereby recommends for examination the dissertation titled "**Paediatric Epilepsy surgery in a middle-income country: The Red Cross War Memorial Children's Hospital experience"**, in partial fulfilment of the requirements for the degree of Master of Medicine (Neurosurgery) of the University of Cape Town.

Dr JMN Enslin

Supervisor

Date: 14/09/2022

Acknowledgement

This work results from the dedication, patience, understanding and selfless guidance of my supervisors, Prof Nico Enslin, Prof Jo Wilmshurst and Prof Graham Fieggen. Special mention to Mr Shaun Linde for his exceptional assistance with the statistical analysis and Dr Christel Arnold-Day for her guidance in compiling the final version of the dissertation.

Dedication

I dedicate this work to my dearest husband, Erno Marais, without whose support and encouragement this work would not have been completed. I appreciate my friends and colleagues for their support during the preparation of this work.

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List of abbreviations

ADEM:	acute disseminated encephalomyelitis
ASM:	antiseizure medication
ATL:	anterior temporal lobectomy
CSF:	cerebrospinal fluid
DNET:	dysembryoplastic neuro-epithelial tumours
EEG:	electroencephalogram
FCD:	focal cortical dysplasia
ILAE:	International League Against Epilepsy
IQR:	interquartile range
LMIC:	Low- and Middle-income countries
MIC:	Middle-income Country
MCD:	malformation in cortical development
MEG:	Magnetoencephalography
MRI:	Magnetic Resonance Imaging
MTS:	mesial temporal sclerosis
PET:	Positron Emission Tomography
PIH:	peri-insular hemispherotomy
RCWMCH:	Red Cross War Memorial Children's Hospital
SEGA:	subependymal giant cell astrocytoma
SPECT	Single-Photon Emission Computerized Tomography
SUDEP:	sudden unexplained death in epilepsy
VNS:	vagal nerve stimulator

Chapter 1: Introduction

Context

Epilepsy is the most common neurological disorder in childhood, affecting 0.5–1% of children under 16 years worldwide.[1] In low- and middle-income countries (LMIC), there is a higher prevalence of epilepsy among children, which may be due to poor antenatal care, nutritional deficiencies, inadequate public sanitation and a more significant proportion of infectious aetiologies. The incidence can be as high as 44 per 1000 children in LMICs [2]

More than half of the patients affected by epilepsy are children, for whom this condition has a significant physical, psychosocial, and economic impact.[3] Uncontrolled seizures affect cognitive and motor development, especially early in life, with recurrent episodes causing pathological changes in healthy and vulnerable brains. These changes are intensified the longer epilepsy remains uncontrolled. This diminishes the capacity of the brain to recover once the seizures are controlled.[3] Recovery of the injured brain depends on pruning and synaptogenesis, which has the most significant capacity early in life. [3] Therefore early control of epilepsy appears to be essential.[4]

Antiseizure medication (ASM) is the first line in managing epilepsy, and while this is effective in most children, a third may have drug-resistant epilepsy.[5] Abnormal neuroimaging is the only independent factor predicting intractability in newly diagnosed childhood epilepsy as only 8.6% of these patients achieve seizure freedom without surgery. [6] Patients with drug-resistant epilepsy are frequently exposed to higher doses of multiple ASMs; these have their complications. Patients with drug-resistant epilepsy have an increased risk of intellectual disability, learning difficulties, physical injuries, sudden unexplained death in epilepsy (SUDEP), psychiatric disorders, and a poorer quality of life.[3]

Epilepsy surgery is potentially curative in patients with drug-resistant epilepsy where the epileptic focus is localised to one area but can be used as a palliative procedure for bi-hemispheric pathology. Epilepsy surgery aims to achieve postoperative seizure freedom; this is possible in 62-74% of patients at five years with cure in 26-57% of cases depending on underlying pathology and location. [7] The term “cure” in epilepsy refers to patients that are rendered free of all seizures for five years without the need to take medication anymore.[8]

Surgery aims to stop developmental regression secondary to drug-resistant seizures and reduce the side effects of ASM by facilitating weaning and cessation of ASM.[3]

While previously epilepsy surgery was viewed as a last resort therapeutic option once all other therapies failed to control drug-resistant seizures, current approaches suggest early epilepsy surgery in managing childhood epilepsy as this is the only treatment option that offers the prospect of cure. This is even more relevant in LMIC, where there is a higher incidence of lesional epilepsy and unreliable availability and access to ASMs.[9] At present, however, there are few studies available addressing the effectiveness, feasibility, and outcome of paediatric epilepsy surgery in an LMIC setting. This study reports on the experience with epilepsy surgery in the paediatric population with drug-resistant epilepsy at Red Cross War Memorial Children's Hospital in Cape Town, South Africa.

Ethical considerations

Ethical approval was obtained from various research committees:

- Step 1: From the Department of Surgery Research Committee at Groote Schuur Hospital,
- Step 2: The University of Cape Town Human Research Ethics Committee (HREC: 140/2020).

Informed Consent process

All data were analysed retrospectively from an anonymised registered patient database (HREC: 140/2020); therefore, a waiver of consent was applied for and granted by the ethics committee. Confidentiality of patient information and data was strictly adhered to and maintained. No identifying personal patient information was required in data analysis or resulted in interpretation.

Author guidelines of the chosen journal

Chosen journal: Journal of Neurosurgery: Pediatrics

The *Journal of Neurosurgery: Pediatrics* is a journal covering topics related to paediatric neurosurgery, it is published by the Journal of Neurosurgery Publishing Group (JNSPG), which began in 2004 and it has become an independent journal since 2008. It is ranked 2333 with a SCImago Journal Rank (SJR) of 1.413, an h-index of 219 and an impact factor of 3.54. ISSN of this journal is/are 0022-3085 (print); 1933-0693 (web).

Journal instructions to authors (Appendix 4)

- Written in UK English in Microsoft word in 12 Times New Roman fonts with 1.5 line spacing.
- Abstract: a 375-word limit
- Article word limit (excluding abstract, tables, figures and bibliography): 4000 words
- Tables and figures allowed: 8
- References: limited to 45
- Authors of original papers are requested to provide the following information: Full qualifications, affiliation and contact details of all authors.
- References: Please follow the *AMA Manual of Style, 11th edition*, for reference formatting (https://www.amamanualofstyle.com).
- Figure Legend: A brief description of each figure, including any figure parts. The significance of any arrows or letters on the figure should be explained, including any abbreviations used.

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Chapter 2: Publication-ready manuscript

Paediatric Epilepsy Surgery in a Middle-Income Country: The Red Cross War Memorial Children's Hospital experience

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Abstract:

Purpose While epilepsy surgery has been shown to reduce seizure frequency and severity and even cures seizures in children with drug-resistant epilepsy, data from middle-income countries (MIC) are lacking.

Method This study is a retrospective review of children with drug-resistant epilepsy who underwent surgical treatment at Red Cross War Memorial Children's Hospital (RCWMCH) between 1 January 2000 and 31 December 2021 (HREC: 140/2020).

Results During the 21-year study period, 60 patients underwent epilepsy surgery for drug-resistant epilepsy. The median age of the children was seven years (IQR 4.81-10.27years) at the time of surgery, with a male predominance of 33 patients. The most common surgical procedure performed was an anterior temporal lobectomy for temporal lobe epilepsy in 19 cases (31.7%), followed by peri-insular hemispherotomy in 9 cases (15.0%) and frontal lobectomy in 8 cases (13.3%). Of the 60 patients, complete records were available for 55 patients noting complications in 11 (20.0%), of which 4 cases (7.3%) had major complications. Notably, 2 patients (3.6%) had new-onset psychiatric symptoms. The long-term outcomes after surgery showed 1-year seizure freedom in 32 patients (58.2%); among these, 21 patients (38.2%) could stop ASM one year after surgery, 17 patients (30.9%) had a recurrence of their seizures, and three had to restart ASM after 2-3 years. Eight patients (14.5%) required repeat surgery. The one-year-Modified Engel scoring for the study population was: 1-A in 52.7%, I-B in 3.6%, I-C in 1.8%, II-A in 15.8%, III-A in 10.9%, IV-A in 3.6% and IV-B in 10.9%. The most common histological finding in anterior temporal lobectomy (ATL) was focal cortical dysplasia (FCD), found in 11 patients (57.9%). The peri-insular hemispherotomy (PIH) cases had equal numbers of FCD and Rasmussen's encephalitis in 4 patients (44.4%). The number of FCD in this series is much higher than in international data.

Conclusion Epilepsy surgery is an effective and attainable intervention for drug-resistant epilepsy in the paediatric population despite limited resources and challenging aetiological profiles. Low complication rates were comparable to international data, with good seizure freedom outcomes.

Keywords: Epilepsy surgery, children, drug-resistant epilepsy, low- and middle-income countries, complications

Introduction:

Epilepsy is a disease where spontaneous recurrent seizures are secondary to abnormal electrical brain activity; the aetiology is complex and multifactorial.[1] Epilepsy is the most common neurological disorder in childhood, affecting 0.5-1% of children under 16 years worldwide.[2] The prevalence of epilepsy is highest among children in low- and middle-income countries (LMIC). This is related to poor antenatal care, neonatal insults, nutritional deficiencies, and prevalent infectious aetiologies. The incidence can be as high as 44 per 1000 children.[3]

Epilepsy has a significant physical, psychosocial, and economic impact on children.[3] Seizures affect cognitive and motor development, especially early in life. Recurrent episodes cause pathological brain changes, which are intensified with prolonged uncontrolled epilepsy. This diminishes the brain's capacity to recover once the seizures are controlled. The ability of the injured brain to recover depends on pruning and synaptogenesis; this has the most significant capacity early in life.[4] Therefore early control of epilepsy is essential.[5]

Antiseizure medication (ASM) is the first line of management for patients with epilepsy. However, a third of children have drug-resistant epilepsy.[1] The International League Against Epilepsy (ILAE) defines drug-resistant epilepsy as the failure to control epilepsy with two sufficient trials of tolerated, appropriately chosen, and used ASM, which can be monotherapy or a combination of ASM.[6] The one factor predicting intractability in newly diagnosed childhood epilepsy is the presence of abnormal brain lesions, e.g. tumours or cortical dysplasia. Only 8.6% of these patients reach seizure freedom without surgery.[7]

Patients with drug-resistant epilepsy are exposed to higher doses of multiple ASMs; these have their complications. Such patients have an increased risk of intellectual disability, learning difficulties, physical injuries, sudden unexplained death in epilepsy (SUDEP), psychiatric disorders, and a poorer quality of life.[4] Subsequent addition of ASMs does not equate to sequential improvement in seizure freedom.[8]

Epilepsy surgery aims to achieve postoperative seizure freedom, which is reported in 62-74% of patients at five years, and cure in 26-57% depending on underlying pathology and location.[9] Cure is defined as seizure freedom for 5-years without medication.[10] Epilepsy

surgery aims to stop developmental regression secondary to refractory seizures and reduce the side effects of medicines by facilitating the weaning of ASM.[3] Surgical outcomes are classified according to the Modified Engel and ILAE classifications (See **Appendix 1**).

Meticulous pre-operative workup and planning by a multidisciplinary team are essential in managing patients with epilepsy. [11] Workup includes thorough clinical examination, epilepsy history, and electroencephalogram (EEG), with clinical correlation for seizure semiology as confirmed during video EEG telemetry with non-invasive or invasive monitoring. Magnetic resonance imaging (MRI) should be performed to identify abnormalities and functional areas mapped with functional MRI, magnetoencephalography (MEG) scan or direct cortical stimulation during surgery or via subdural EEG grids. Neuropsychological assessments can be helpful to assess the pre-operative cognitive and functional abilities, as well as monitor postoperative changes.[12]

The surgical technique (resections, disconnection and/or neuromodulation) and approaches are individualised to the underlying pathology and region affected.[4] Intra-operative resection should incorporate wide resection of the seizure onset zone, the irritative zone, and the cortical spread pattern.[11] Complete resection of the electrographic abnormality (both the seizure generating zone and the seizure network) is the most important predictor of overall seizure freedom.[13] Other factors associated with favourable outcomes are younger age at surgery, unifocal lesions, absence of contralateral EEG abnormalities and specific pathologies, e.g. glioneural tumours.[4]

Epilepsy surgery has relatively low complication rates. Hader et al. divided the complications into minor and major medical and neurological complications.[14] The minor medical complications reported in 5.1% of patients include cerebrospinal fluid (CSF) leaks, aseptic meningitis, bacterial infections, and intracranial haematomas. The major medical complications reported are less common ($\leq$1%) and include hydrocephalus and intracranial abscesses. Minor neurological complications usually resolve and are reported in 10.9% of patients, e.g. minor visual field defects, transient dysphasia, transient hemiparesis and minor psychiatric disturbances. Major neurological complications are reported in 4.7% of patients and usually do not resolve, e.g. permanent hemiparesis and significant psychiatric disorders. Large studies report perioperative mortality in 0.6% of patients.[14] Therefore, epilepsy surgery is relatively safe compared to many other neurosurgical procedures.

Drug-resistant epilepsy is associated with high costs and significant economic sequelae for the family due to frequent hospital admissions and expenses of ASM. Epilepsy surgery is a cost-saving intervention that reduces these costs.[15]

This study aimed to demonstrate that epilepsy surgery is possible and safe in a Middle-Income Country (MIC) setting. Limited data exist on the effectiveness, feasibility, and outcome of paediatric epilepsy surgery in a MIC environment. This study reports the experience of epilepsy surgery in the paediatric population with drug-resistant epilepsy at Red Cross War Memorial Children's Hospital (RCWMCH) in Cape Town, South Africa.

Methods:

Study setting and patient selection

This is a retrospective descriptive study of all children with drug-resistant epilepsy who underwent epilepsy surgery at RCWMCH between 1 January 1983 and 31 December 2021 with four different surgeons in the various periods (WP, JCP, AGF, and NE). To ensure more homogeneity, detailed discussion and analysis was done on the group from 1 January 2000 to 2021. These dates align to when a formal program for epilepsy surgery workup was initiated by paediatric neurology, and detailed records were available. The patients were identified from neurosurgical theatre records of all procedures performed during the study. Patient demographics i.e. gender, age at surgery and delay in surgery, were assessed in order to compare it to other studies and to see if there's a correlation with outcome. Surgical procedures, complications and essential outcome data were collected from patient records. Post-operative seizure outcome was collected from patient records at follow-up visits one year after surgery. The results were graded according to the Modified Engel Classification (see **Appendix 1**).

Presurgical evaluation and selection for surgery

Epilepsy semiology and diagnoses were confirmed by in-patient EEG, telemetry, and pre-operative MRIs. Where indicated, patients underwent video-telemetry to correlate the lesion location to the seizure semiology. Subdural grids were implanted where EEG and imaging findings were incongruent, or the team raised specific functional or network-related questions. This localised the epileptogenic zone and aided in evaluating the epileptogenic

network. Surgical procedures were recorded in theatre records, and complications were documented in patients' records. Outcomes of the subdural grid placements were also recorded. If the epileptogenic zone was in the eloquent cortex, a pre-operative functional MRI or intra-operative cortical stimulation was done to plan surgical resection (awake surgery in children older than eight years if tolerated, otherwise, pre-operative grid placement and cortical stimulation were performed before surgery).

Surgical approach and histological classification

Surgical approaches and intra-operative findings were obtained from theatre records and operation notes in patients' records. Histological diagnoses were obtained from the National Health Laboratory Services.

Surgical outcomes

Surgical complications were collected from patient records. Specifically, to assess changes in neurological deficits, and comparisons were made from pre-operative, immediate postoperative and follow-up neurological assessments done at follow-up clinics post-discharge. Routine postoperative imaging (mainly CT scan in the immediate post-operative period and MRI after three months) was also evaluated. This permitted longitudinal monitoring of neurological changes and established if the neurological deficit was new, transient, or permanent. These were categorised based on whether the neurological deficit was expected (as in the contralateral hand weakness that is permanent after hemispherotomy) or unexpected (such as leg weakness after an anterior temporal lobectomy).

Seizure control was classified according to the Modified Engel classification (see **Appendix 1**) based on the information provided during the 1-year follow-up visits.

Statistical analyses

Confidentiality of patient information was strictly adhered to and maintained. No identifying demographic information was required in data analysis or resulted in interpretation. This study was approved by the University of Cape Town's human research ethics committee (HREC: 140/2020). A database was created with all the data collected from the folders. Descriptive analysis was done using Microsoft Excel's statistical functions. No specific tests were used in this study as it was descriptive.

Results:

Demographic data

Table 1: Demographic data of patients who had epilepsy surgery at RCWMCH from 01 January 2000 to 31 December 2021

	Epilepsy Surgery N (%)
Total	60
Gender	
Total (N)	60
Male	33 (55.0)
Female	27 (45.0)
Age at Onset (Years)	
Total (N)	50
Median (IQR)	5.00 (3.00-7.00)
Range	0-13.0
Missing	10 (16.7)
Age at Surgery (Years)	
Total (N)	60
Median (IQR)	7.31 (4.81-10.27)
Range	0.04-15.20
Duration from diagnosis till surgery (Years)	
Total (N)	50
Median (IQR)	3.61 (1.34-4.60)
Range	0-11.9
Missing data	10 (16.7)

The demographic data and study cohort is described in **Table 1.** A total of 60 cases were operated on, of which 55% were male; the median age at surgery was seven years and a median time of 3.6 years from diagnosis until surgery was found.

Invasive pre-operative evaluation

Nine subdural grids were implanted as part of the pre-operative work-up. In this group, median age at time of surgery was five years (IQR 4-6). Seven patients underwent epilepsy

surgery after subdural grids monitoring and the epileptogenic area localised. Of the two patients who did not proceed with epilepsy surgery, one patient's family declined surgery and the other patient showed incongruence between EEG changes and seizures. Four of the seven children who underwent epilepsy surgery had ASM stopped by 1-year post-surgery (57.1%). Two patients required repeat surgery due to seizure recurrence, and one had improved seizure control. Only two complications were reported from the nine procedures, including a CSF leak without the development of meningitis and intra-operative bleeding from the skin flap requiring a blood transfusion in theatre.

Surgical approaches

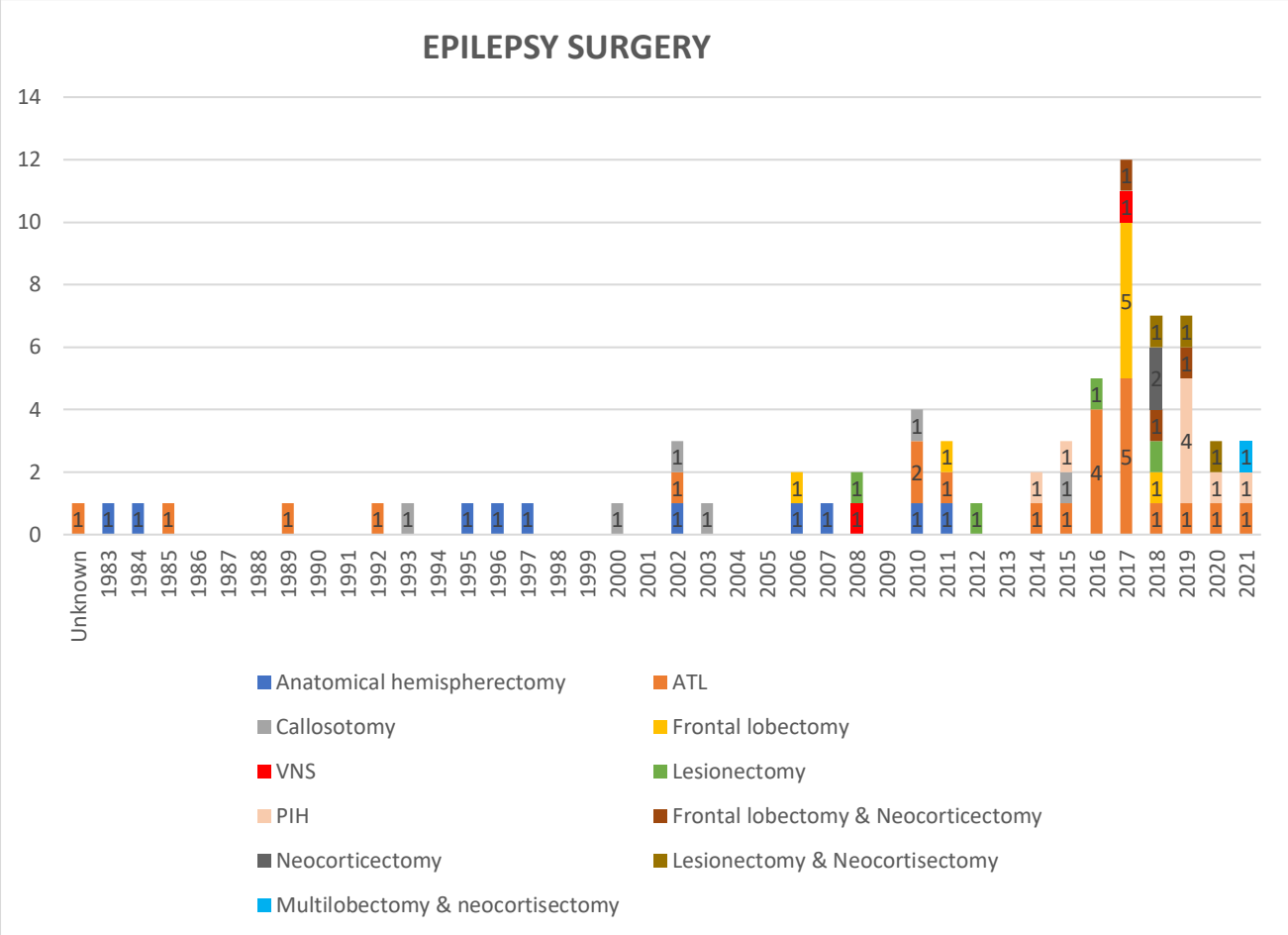

Figure 1: Distribution of frequency and type of epilepsy surgeries performed from the 1st of January 1983 till the 31st of December 2021.

ATL= Anterior temporal lobectomy; VNS= Vagal Nerve Stimulator; PIH= Peri-insular hemispherotomy

Figure 1 illustrates that although epilepsy surgery commenced in 1983, initially procedures were few and far between. A dedicated paediatric neurologist joined the program in 2000, which enabled a multidisciplinary approach to evaluating suitable cases from this time. The epilepsy surgery program further intensified in 2010, driven by increased access to video-EEG and MRI|, with a variety of procedures performed at increasing intervals and formalised planning epilepsy surgery MDTs from 2015 onwards. COVID-19 theatre restrictions led to decreased cases over 2020 – 2021. Four surgeons performed epilepsy surgery over the past 39 years, i.e., WP from 1983 to 1986; JCP from 1987 to 1999; AGF from 2000 to 2014; NE from 2015 onwards.

Table 2: Surgical procedures performed as part of the RCWMCH's epilepsy program from 1 January 2000 till 31 December 2021.

Procedure Category	N (%)
Total	60
ATL	19 (31.7)
PIH	9 (15.0)
Anatomical Hemispherectomy	4 (6.7)
Frontal Lobectomy	8 (13.3)
Corpus Callosotomy	5 (8.3)
Lesionectomy	5 (8.3)
Lesionectomy & Neocorticectomy	3 (5.0)
Neocorticectomy	2 (3.3)
VNS	2 (3.3)
Frontal Lobectomy & Neocorticectomy	2 (3.3)
Neocortisectomy & Multilobar Resection	1 (1.7)

ATL= Anterior temporal lobectomy; VNS= Vagal Nerve Stimulator; PIH= Peri-insular hemispherotomy

Table 2 shows the types of surgical procedures performed from 1 January 2000 to 31 December 2021. The most common approach was an anterior temporal lobectomy (ATL) (31.7%), followed by peri-insular hemispherotomy (PIH) (15.0%) and frontal lobectomy (13.3%). The first PIH was performed in 2011 and replaced anatomical hemispherectomy.

Surgical outcomes: Epilepsy control

Table 3: Surgical procedure with related surgical outcomes - epilepsy control

	I.A N (%)	I.B N (%)	I.C N (%)	II.A N (%)	III.A N (%)	IV.A N (%)	IV.B N (%)	Total N (%)
All cases	29	2	1	9	6	2	6	55
Procedure Category								
PIH	5 (17.2)	1 (50.0)	0 (0)	1 (11.1)	1 (16.7)	1 (50.0)	0 (0)	9 (15.8)
Anatomical Hemispherectomy (Missing data = 2)	0 (0)	0 (0)	0 (0)	1 (11.1)	0 (0)	0 (0)	1 (16.7)	2 (3.6)
ATL (Missing data = 1)	10 (34.5)	0 (0)	1 (100)	4 (44.4)	1 (16.7)	0 (0)	2 (33.3)	18 (32.7)
Corpus Callosotomy (Missing data = 1)	3 (10.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.7)	4 (7.3)
Frontal Lobectomy	5 (17.2)	0 (0)	0 (0)	0 (0)	1 (16.7)	1 (50.0)	1 (16.7)	8 (14.0)
Lesionectomy (Missing data = 1)	3 (10.3)	0 (0)	0 (0)	1 (11.1)	0 (0)	0 (0)	0 (0)	4 (7.0)
Neocorticectomy	1 (1.8)	0 (0)	0 (0)	1 (11.1)	0 (0)	0 (0)	0 (0)	2 (3.5)
VNS	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.7)	0 (0)	1 (16.7)	2 (3.5)
Frontal Lobectomy & Neocorticectomy	0 (0)	0 (0)	0 (0)	1 (11.1)	1 (16.7)	0 (0)	0 (0)	2 (3.5)
Lesionectomy & Neocortisectomy	2 (3.5)	0 (0)	0 (0)	0 (0)	1 (16.7)	0 (0)	0 (0)	3 (5.3)
Neocortisectomy & Multilobar Resection	0 (0)	1 (50.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.8)
Total	29 (52.7)	2 (3.6)	1 (1.8)	9 (15.8)	6 (10.9)	2 (3.6)	6 (10.9)	55
Missing data								5 (8.3)

ATL=Anterior temporal lobectomy; VNS= Vagal Nerve Stimulator; PIH= Peri-insular hemispherotomy

Missing data in 5/60 patients (8.3%) was due to destroyed hospital records or lack of follow-up data. Therefore 55 surgical cases were analysed for post-operative epilepsy control. As evident from **Table 3**, epilepsy surgery had a good outcome. The minority of patients had no

worthwhile response, two patients (3.6%) with an Engel score of IV-A and six patients (10.9%) with IV-B. All other surgical procedures showed a higher percentage improvement in epilepsy control, except for the vagal nerve stimulator (VNS) cases, which had equivocal results.

Table 4: Long-term outcomes of epilepsy surgery

	Meds Weaned		Recurrence		Repeat Surgery	
	Yes	**No**	**Yes**	**No**	**Yes**	**No**
Number	21	34	17	38	8	47
Procedure Category						
Hemispherotomy PIH N (%)	4 (19.0)	5 (14.7)	2 (11.8)	7 (18.4)	0 (0)	9 (19.1)
Hemispherectomy Anat N (%)	0 (0)	2 (5.9)	1 (5.9)	1 (2.6)	0 (0)	2 (4.3)
ATL N (%)	8 (38.1)	10 (29.4)	8 (47.1)	10 (26.3)	4 (50.0)	14 (29.8)
Corpus Callosotomy N (%)	1 (4.8)	3 (8.8)	0 (0)	4 (10.5)	0 (0)	4 (8.5)
Frontal Lobectomy N (%)	2 (9.5)	6 (17.6)	0 (0)	8 (21.1)	0 (0)	8 (17.0)
Lesionectomy N (%)	2 (9.5)	2 (5.9)	4 (23.5)	0 (0)	3 (37.5)	1 (2.1)
Neocortisectomy N (%)	1 (4.8)	1 (2.9)	1 (5.9)	1 (2.6)	0 (0)	2 (4.3)
VNS N (%)	0 (0)	2 (5.9)	0 (0)	2 (5.3)	0 (0)	2 (4.3)
Frontal Lobectomy & Neocortisectomy N (%)	1 (4.8)	1 (2.9)	1 (5.9)	1 (2.6)	1 (12.5)	1 (2.1)
Lesionectomy & Neocortisectomy N (%)	2 (9.5)	1 (2.9)	0 (0)	3 (7.9)	0 (0)	3 (6.3)
Neocortisectomy & Multilobar Resection N (%)	0 (0)	1 (2.9)	0 (0)	1 (2.6)	0 (0)	1 (2.1)
Total N (%)	21 (38.2)	34 (61.8)	17(30.9)	38 (69.1)	8 (15.8)	47 (84.2)
Missing data N (%)	5 (8.3)		5 (8.3)		5 (8.3)	

ATL= Anterior temporal lobectomy; VNS= Vagal Nerve Stimulator; PIH= Peri-insular hemispherotomy

Many seizure-free patients off ASM were lost to follow-up after one year, and long-term seizure outcomes and cure could not be evaluated. **Table 4** illustrates the long-term outcomes of epilepsy surgery. This analysis was performed on 55 surgical cases due to missing data in 5 surgical cases (8.3%).

As illustrated in Tables 3 and 4, PIH had good postoperative results. Eight patients (88.9%) responded well to surgery, with six patients (66.7%) completely seizure-free, of which four (44.4%) patients ASMs could be stopped by 1-year post-surgery, and two patients (22.2%) had improvement in their epilepsy control. Two patients (22.2%) had seizure recurrence, but no repeat surgery was required. Eighteen cases that underwent ATL were analysed with missing data in one patient. Eleven patients (61.1%) had complete seizure freedom at 1-year, eight patients (44.4%) could stop their ASM by 1-year post-surgery, and five patients (27.8%) had improvement in their epilepsy control. Eight patients (44.4%) had seizure recurrence, three had to restart ASM 2 to 3 years after surgery, and four (22.2%) required repeat surgery. This was all in cases of widespread focal cortical dysplasia where anatomical landmarks limited the initial resection.

Histological findings

Table 5: Histological diagnoses with breakdown found in the different surgeries

	PIH N (%)	**AH N (%)**	**ATL N (%)**	**CL N (%)**	**FL N (%)**	**Les N (%)**	**Neo N (%)**	**FL & Neo N (%)**	**Les & Neo N (%)**	**ML & Neo N (%)**	**Total N (%)**
Total N	**9**	**3**	**19**	**3**	**8**	**5**	**2**	**2**	**3**	**1**	**55**
Histology Category											
FCD	4 (44.4)	2 (66.7)	11 (57.9)		5 (62.5)		1 (50)	2 (100)	2 (66.7)	1 (100)	**28 (50.9)**
○ **FCD type I and II**	3 (33.3)	1 (33.3)	7 (36.8)		3 (37.5)			2 (100)	1 (33.3)	1 (100)	**18 (32.7)**
○ **FCD** type 3	1 (11.1)	1 (33.3)	4 (21.1)		2 (25.0)		1 (100)		1 (33.3)		**10 (18.2)**
• ***MTS & FCD 3***		1	1								2
• ***DNET & FCD 3***			1								1
• ***Ganglioglioma & FCD 3***			2		1				1		4

	PIH N (%)	AH N (%)	ATL N (%)	CL N (%)	FL N (%)	Les N (%)	Neo N (%)	FL & Neo N (%)	Les & Neo N (%)	ML & Neo N (%)	Total N (%)
• ***ADEM & FCD 3***					1						1
• ***Encephalitis NOS & FCD 3***							1				1
• ***Rasmussen's & FCD 3***	1										1
DNET			3 (15.9)		2 (25.0)	2 (40)	1 (50)		1 (33.3)		**9 (16.4)**
Ganglioglioma	1 (11.1)		5 (26.3)		1 (12.5)	2 (40)			1 (33.3)		**10 (18.2)**
Rasmussen's Encephalitis	4 (44.4)	1 (33.3)	1 (4.8)	1 (33.3)							**6 (10.9)**
MTS		1 (33.3)	4 (19.0)			1 (20)					**6 (10.9)**
SEGA					1 (12.5)						**1 (1.8)**
ADEM					1 (12.5)						**1 (1.8)**
Encephalitis NOS				2 (66.7)			1 (50)				**3 (5.5)**
Normal brain	1 (11.1)										**1 (1.8)**
Missing data	0	1 (25.0)	0	2 (71.4)	0	0	0	0	0	0	**3 (5.2)**
No Histology taken: VNS placement											**2**

PIH= Peri-insular hemispherotomy; AH= Anatomical hemispherectomy; ATL= Anterior temporal lobectomy; CL= Callosotomy; FL= Frontal lobectomy; Les= Lesionectomy; Neo= Neocorticectomy; ML= Multilobectomy; DNET= Dysembryoplastic neuro-epithelial tumours; FCD= Focal cortical dysplasia; MTS= Mesial Temporal Sclerosis; SEGA= Subependymal giant cell astrocytoma; ADEM= Acute disseminated encephalomyelitis; NOS= Not otherwise specified.

The histological spectrum from our series was widespread; these results can be seen in **Table 5**. Fifty-eight surgical cases were evaluated as the VNS patient had no histology taken; data were incomplete for three surgical cases (5.2%); therefore, 55 cases were analysed. The most common histological diagnosis was FCD (50.9%); type I and II were found in 18 patients (32.7%) and type III in ten patients (18.2%). As seen in table 5, Types I and II were most commonly found in ATL, PIH and frontal lobectomy cases, while type III was most

commonly found in ATL. This was followed by ganglioglioma (18.2%) and dysembryoplastic neuro-epithelial tumours (DNET) in 16.4%.

Complications related to surgery

Table 6: Complications related to the surgical procedures performed

	PIH	Anatomical hemispherotomy	ATL	Frontal lobectomy	Lesionectomy	Callosotomy	Total
Total surgeries N	8	3	19	8	4	3	55
Minor wound related complications	0	0	0	0	1	0	1 (1.8)
ICH	0	1	0	0	0	0	1 (1.8)
Nosocomial sepsis	1	0	0	0	0	0	1 (1.8)
Infarct without clinical significance	1	0	0	0	0	0	1 (1.8)
Transient motor deficit	0	0	1	0	0	0	1 (1.8)
Transient aphasia	0	0	1	0	0	0	1 (1.8)
Transient visual field defect	0	0	1	0	0	0	1 (1.8)
Hypeaccusis	0	0	0	0	1	0	1 (1.8)
Overall N(%)	**2 (3.6)**	**1 (1.8)**	**3 (5.5)**	**0 (0.0)**	**2 (3.6)**	**0 (0.0)**	**8 (14.5)**
Hydrocephalus	1	0	0	0	0	0	1 (1.8)
Infarct with resultant permanent motor deficit and dystonia	0	0	1	0	0	0	1 (1.8)
Psychiatric complication	0	0	1	1	0	0	2 (3.6)
Overall N (%)	**1 (1.8)**	**0 (0.0)**	**2 (3.6)**	**1 (1.8)**	**0 (0.0)**	**0 (0.0)**	**4 (7.3)**
Missing data N (%)	**1 (12.5)**	**1 (25.0)**	**0 (0.0)**	**0 (0.0)**	**1 (20.0)**	**2 (40.0)**	**5 (8.3)**
Total procedures with complications N (%)							**11 (20.0)**

Complications could be analysed for 55 patients as data was missing for five patients (8.3%). The anticipated sequelae (such as transient hemiparesis with perirolandic lesions) were not included in the complications. These expected post-operative findings included hemiplegia, transient aphasia and hemianopia with a hemispherotomy. No complications were reported in 44/55 epilepsy surgeries (80%). The other 11 patients had 12 complications reported, with an overall complication rate of 20%, (**Table 6).** Only 7.3% of the complications were major complications. The minor complications (14.8%) were transient and did not require significant medical intervention. The major complications required significant surgical or medical intervention or caused permanent neurological deficits. Two patients had new onset psychiatric complications (3.6%) that could be controlled with medication. The procedure with the most complications reported was ATL, with three minor and two major complications (9.1%). The peri-operative mortality rate was 0%.

Discussion:

This study population had a male predominance, with median seizure onset of five years of age and median time of surgery of 7 years of age. Lamberink et al. also reported a predominantly male population, although their median seizure onset was 10 years.[9] This is likely to depend on aetiology, as FCD had a median seizure onset of 3 years of age, whilst for low-grade tumours, it was 11 years.[9] RCWMCH had a median delay in surgery of only 3,6 years from epilepsy onset. These results compare favourably to others that reported an average of 5-10 years between diagnosis and surgery.[9] This is encouraging since Braun noted that delay in surgery for longer than five years decreases seizure freedom at five years from 66% to 31%.[7] This might be because the child neurologists at RCWMCH strategically manage children within a dedicated epilepsy service and identify drug-resistant patients at the earliest possible stage; secondly, the impact of transport difficulties and distance to travel mean that patients are more likely to be admitted for focused work-up, thereby shortening work-up time considerably. Lastly, the region has few dedicated paediatric epilepsy facilities, so direct referrals from all levels of care are common. As a multidisciplinary team, management decisions regarding surgical treatment as an option are discussed while the patient is still in the hospital. This streamlined approach is probably beneficial in reducing the duration of uncontrolled seizures and subsequent impact on neurodevelopment.

The cost of treatment escalates when invasive monitoring is done. Invasive EEG monitoring has not been used frequently at RCWMCH and was only required in 9/60 epilepsy surgeries. However, the benefit of invasive EEG monitoring techniques when indicated is undeniable; four patients were off ASM by 1-year post-op in cases where it was used. One patient was averted from having surgery that could have resulted in surgery in a location that was proven not to be the electrical focus of the seizures, and the associated complications were low. It is, however, essential to utilise invasive EEG as indicated in standardised protocols and appreciate that no single investigative modality can dictate surgical approach, the extent of resection or predicts the surgical outcome, but rather a combination of multiple investigative modalities, expert interpretation and a skilled multidisciplinary team trained in the field of functional epilepsy surgery, that drives the success of these procedures.

Eleven categories of procedures were performed at RCWMCH during the study period. The most common approach was an ATL (31.7%), followed by PIH (15.0%) and frontal lobectomy (13.3%). This observation compares well with the ILAE survey from 2004, which showed that 23.2% ATL, 15.8% PIH and 17.8% frontal lobectomies were performed.[16] This may reflect the high rate of focal cortical dysplasia and other developmental anomalies encountered in Africa.

Rates of seizure control after epilepsy surgery were reasonable. The seizure freedom at one year was attained in 32/55 cases analysed (58.2%), of which 21 (38.2%) patients' ASMs could be stopped one year postoperatively. These patients had well-defined epileptogenic zones corresponding with the pathology, and the appropriate surgery was well executed. The patients with recurrences had either more than one epileptogenic focus, not addressed by the initial surgery, or a lesion was not completely resected with the initial surgery. With the eight reoperated patients, the residual pathology was addressed, e.g. residual DNET, ganglioglioma and MTS, and ASM were stopped. FCD type 1 patients were more difficult to control, and some required more than one surgery to improve seizure control.

Only 15.8% of patients showed no improvement in seizure control. 75% of these patients had FCD and a change in epileptic focus pattern, initially only involving a focal area but later the entire hemisphere. This data showed slightly lower seizure freedom than the international data reported by Widjaja, which reported 1-year seizure freedom of 64.8%. This study also noted that the seizure-freedom rate reduces over time, 60.3% at five years and 39.7% at ten

years. The differences in histopathological profile compared to the patient profile in Widjaja's analysis consisted of 32% FCD, compared to the 50.9% in our study population.[17] According to Lamberlink, seizure-freedom rates with FCD can be as low as 51.9%. This indicates that FCD provides more challenges in epilepsy surgery. Lesions like DNET, gangliogliomas, and MTS are well defined and easier to resect completely than FCD. Secondly, FCD can change the epileptogenic focus, causing recurrence if not detected initially. It is essential for complete resection of the epileptogenic- and irritative zones to ensure seizure freedom. However, if epilepsy surgery is done for the correct indication, most patients will improve and derive benefits from these types of procedures. This study also showed similar results as those reported by other international institutions despite resource constraints and more challenging pathology.

Of the nine patients that underwent PIH, 6 (66.6%) had 1-year seizure freedom and in 4 (44.4%) patients, ASM could be stopped by 1-year post-surgery. Two patients (22.2%) had a recurrence of seizures. These patients had seizures on the ipsilateral side of the surgery post-operatively, and whether it was seizures or psychogenic non-epileptogenic seizures could not be confirmed. Therefore, recurrence is questionable. None of these patients required repeat surgery. Ji et al. reported in a recent PIH study that seizure-freedom rates after four years were 83.1%, and 16.9% had recurrent seizures.[18] This study's seizure-freedom rate is lower than Ji's. A possible explanation for the difference in seizure-freedom rates is our study's percentage of developmental pathology (60%) compared to 27% in Ji's. Villemure demonstrated that acquired conditions have a higher success rate than developmental pathology.[19]

ATL had 1-year seizure freedom of 58.2%, with 38.2% of patients who could stop their ASM by one-year post-surgery, while 14.5% required repeat surgery. These patients had multiple epileptogenic foci or were more diffuse, and the ATL did not resect the entire area. Zupanc reported the 1-year seizure freedom to be 84.2% after ATL, which was significantly better, but the incidence of MTS was much higher, with a higher success rate.[20] MTS is not common in children. The patients who had repeat surgery with resection of the recurrent or residual lesion had good seizure control post-operatively. It is, therefore, crucial to determine the extent of the epileptogenic zone pre-operatively to attain seizure freedom. Unfortunately, it is not always possible to resect the entire epileptogenic area as this might cause significant

neurological deficits. Therefore, the risk-benefit ratio between neurological deficits, seizure control and recurrence should be considered before surgery.

FCD was the most common pathology found to cause drug-resistant epilepsy (50.8%); Lamberink's observations showed that only 19% of the cases were due to FCD, with hippocampal sclerosis being the most common pathology (35.6%).[8] Most patients who required repeat surgery had FCD, which suggests how challenging it is to resect the entire lesion. This may explain why this study's seizure-freedom rate was lower than in international studies. Bourgeois reported a 61.2% 10-year seizure-freedom rate if the lesion was resected completely.[21]

Twelve complications were reported in 11/55 surgical cases (20.0%), classified into minor (14.5%) and major complications (7.3%). The minor complications were similar to those reported by Hader (16.8% vs 14.5% observed in this study. The major complications were also similar at 7.3% compared to the 5.7% in Hader's study. [14]). Hydrocephalus, requiring a ventriculoperitoneal shunt, occurred in 1 patient who underwent a PIH. Many epilepsy units place an external ventricular drain (EVD) as standard practice after a PIH. Despite not following this practice, the incidence of hydrocephalus did not increase. The small basal ganglia infarct was due to a suspected choroidal artery spasm in a medial temporal ganglioglioma. This caused persistent mild hemiparesis and dystonic foot posturing. These tumours are often adherent to the Sylvian fissure branches, which may lead to spasms with manipulation. As reported by Boucher et al., hyperacusis is an infrequent complication in epilepsy surgery due to damage to the insular cortex.[22] The finding is in keeping with the surgical approach targeting the Sylvian fissure lesion.

Five complications (9.1%), of which two (3.6%) were major, were reported in the ATL patients. According to Villemure, the incidence of complications in their study was 9.3%.[19] This complication rate is very similar to international data.

Epilepsy surgery in our setting led to a 1-year seizure-freedom of 58.2% and allowed 38.2% of patients to stop their ASM by 1-year post-surgery. This could potentially lead to fewer presentations and admissions to hospitals and emergency units; even though this was not investigated in this study, it is a conclusion that can be drawn. Over time epilepsy surgery is a

cost-saving intervention that can improve quality of life and prevent long-term neurological sequelae for patients with drug-resistant epilepsy.

In previous decades, epilepsy surgery was seen as the last resort, a desperate attempt to control drug-resistant epilepsy. As illustrated in **figure 1**, this data shows that sporadic surgeries were performed in the initial period of the epilepsy surgery program until the epilepsy surgery service started gaining momentum in 2010. Potential factors include an increase in evidenced-based practice supporting earlier consideration for surgical management as this leads to better seizure control whilst mitigating the potential neurological damage associated with drug-resistant epilepsy. Other factors driving this change could also include strengthening experience and building a well-established network of specialised multidisciplinary team members working to develop a reliable epilepsy surgery service.

Conclusion

Patients who underwent epilepsy surgery for drug-resistant epilepsy from 1 January 2000 until 31 December 2021 at RCWMCH had a 1-year seizure-freedom rate of 58.2%, slightly lower than international data, possibly due to the higher incidence of FCD. The most common procedure was an anterior temporal lobectomy. The neurological complications for all epileptic surgeries performed at RCWMCH were similar to internationally published data.

Epilepsy surgery is an effective and attainable treatment option for treating drug-resistant epilepsy in paediatric patients in resource-constrained environments. Despite the limited resources, the complication rates are similar to those reported internationally. The establishment of a dedicated team is essential to make this successful.

Future research should include a cost-benefit analysis in a middle-income country, as well as detailed prospective analysis of cognitive and seizure freedom outcomes in children in LMIC's.

Strengths

This is the first dataset on paediatric epilepsy surgery from sub-Saharan Africa in the public hospital setting to provide data from a resource-constrained setting regarding demographic data, surgical procedures performed and long-term outcomes on seizure control in a MIC.

Limitations

This is a retrospective review study and presented with challenges commonly associated with such databases, such as missing information. There is also an inherent inclination for recall bias in such studies; therefore, the findings must be interpreted in this context. Cognitive outcomes could not be analysed due to the limited neurocognitive assessments done as part of the pre-operative work-up, although this is now standard practice. Patients with epilepsy are managed at RCWMCH until they are seizure-free or complete educational placement. Therefore, seizure-free patients and those off medication are not followed up for five years, and some with relapses might have been missed.

Author contributions

LL and JMNE collected, coded and cleaned the data. LL, JMNE and SL analysed the data. All authors had access to the dataset, assisted with data review and preparation, critiqued and approved the final manuscript.

Declaration of conflicting interest

The authors declare no potential conflicts of interest concerning this article's research, authorship, and/or publication.

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Appendices

Appendix 1: A comparison between the Modified Engel Classification and ILAE Classification of postoperative seizure outcome.[23]

Engel classification	ILAE classification
Class I. Free from disabling seizures	**Class 1**. Completely seizure free; no auras Class 1a. Completely seizure free since surgery; no auras **Class 2.** Only auras; no other seizures
A. Completely seizure free since surgery	
B. Nondisabling simple partial seizures only since surgery	
C. Some disabling seizures after surgery, but free from disabling seizures for ≥2 years	
D. Generalized convulsions w/AED discontinuation only	
Class II. Rare disabling seizures (almost seizure free)	**Class 3**. 1–3 seizure days/year; ±auras
A. Initially free from disabling seizures, but still has rare seizures	
B. Rare disabling seizures since surgery	
C. Occasional disabling seizures since surgery, but rare seizures for the last 2 years	
D. Nocturnal seizures only	
Class III. Worthwhile improvement	**Class 4**. 4 seizure days/year—50% reduction in baseline no. of seizure days; ±auras
A. Worthwhile seizure reduction	
B. Prolonged seizure-free intervals amounting to >50% of follow-up period, but not <2 years	
Class IV. No worthwhile improvement	**Class 5**. <50% reduction in baseline no. of seizure days – 100% increase in baseline no. of seizure days; ±auras
A. Significant seizure reduction	
B. No appreciable change	
C. Seizures worse	**Class 6**. >100% increase in baseline no. of seizure days; ±auras

Appendix 2: Department of Surgery Research Committee Ethical approval

UNIVERSITY OF CAPE TOWN

Department of Surgery
Departmental Research Committee
Dr Timothy Pennel
D24 Office, Groote Schuur Hospital
Observatory 7925
South Africa
Tel (021) 404 3430
Email: tim.pennel@uct.ac.za

20 Jun 2019

Dr L Louw

Department of Surgery
University of Cape Town

Dear Dr Louw

RE: Project 2019/055

PROJECT TITLE: The Management Of Epilepsy Due To Low Grade Neuroepithelial Tumours In The Paediatric Population: Comparing The Outcomes Of Different Management Paradigms

The above protocol has been reviewed by the Department of Surgery Research Committee. I am pleased to inform you that the committee approved the scientific merit of the study, and endorse the protocol for submission to the relevant ethics committee.

Although this letter serves as confirmation that the above protocol has successfully passed through the surgical DRC, respective ethics committees still require DRC chair signature before submission.

Please use the above project number in all future correspondence,

Yours sincerely

Officially signed

DR TIMOTHY PENNEL
CHAIRMAN: RESEARCH COMMITTEE

"OUR MISSION is to be an outstanding teaching and research university, educating for life and addressing the challenges facing our society."

Appendix 3: Human Research Ethics Committee approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

11 March 2020

HREC REF:140/2020

Dr J Enslin
Division of Neurosurgery
Department of Paediatric Surgery
6th Floor, ICH Building
Red Cross War Memorial Children's Hospital
Rondebosch

Dear Dr Enslin

PROJECT TITLE: RETROSPECTIVE REVIEW OF CHILDREN DIAGNOSED WITH LOW GRADE CEREBRAL TUMOURS AT RED CROSS CHILDREN'S HOSPITAL (MMED DEGREE - DR LIZET LOUW)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 March 2021.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Dr Lizet Louw will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

Singed by officials

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

HREC 140/2020sa

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HUMAN RESEARCH ETHICS COMMITTEE
14 MAR 2022
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

UNIVERSITY OF CAPE TOWN FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) This serves as notification of annual approval including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.3.23
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee	Officially signed	Date Signed	15/3/22

Note: Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.
Please clarify your plan for research-related activities during COVID-19 lockdown.
Please use the latest form found on our website:
http://www.health.uct.ac.za/fhs/research/humanethics/forms

Comments to PI from the HREC
Thank you for your Study Deviation officially signed HREC Chair Sig... Date: 15/3/22

Principal Investigator to complete the followin

1. Protocol Information

Date (when submitting this form)	07/03/2022		
HREC REF Number	140/2020	Current Ethics Approval was granted until	30/03/2021
Protocol title	Retrospective review of children diagnosed with low grade cerebral lesions at Red Cross Children's Hospital (MMed degree Dr Lizet Louw)		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	☐ Yes	☐ No X	
If yes, could you please provide the HREC Reference number for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	DR JMN Enslin		

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Appendix 4: General author guidelines (journal)

JNSPG Manuscript Limits Policy

Requirements for Authors

In addition to adhering to the limits outlined in the Manuscript Limits table, authors ***must list*** counts for the following items on the title page of the manuscript:

- Abstract word count
- Text word count
- Number of references
- Number of tables and/or figures (total)
- Number of videos

When submitting revisions, authors ***must update*** the counts on the title page of the manuscript. See the manuscript template Word file, available for download from the Author Instructions tab of the submission site.

Peer-review staff will verify that the limits are not exceeded.

Manuscript Limits

Journal of Neurosugery, Journal of Neurosurgery: Spine, Journal of Neurosurgery: Pediatrics

Article Type	Definition	Abstract*	Text*	Tables & Figures†	Videos	References
Clinical article	Original research in 5 or more human subjects	375‡	4000	8	2	45
Laboratory investigation	Original research in cadavers, animals, cell lines, or basic science	375‡	4000	8	2	45
Literature review (including systematic review)	Reviews and/or meta-analyses of neurosurgical topics or large indexing databases (e.g., PubMed, EMBASE)	375	4000	8	2	75
Technical note	Description of a novel procedure or technique	200	2500	5	2	45
Historical vignette	Reporting on the neurosurgical significance of an event, person, or period in history	200	3500	8	2	45
Opinion piece		NA	3500	5	2	45
Letter to the Editor or response	Comments on an article published in a JNSPG journal within the 2 years prior to submission of the letter	NA	500	1 figure or 1 table or 1 video		10

Other JNSPG journals

Article Type	Definition	Abstract*	Text*	Tables & Figures†	Videos	References
Neurosurgical Focus	Topic-based articles	375	3500	8	2	75
Neurosurgical Focus: Video¶	Topic-based video articles	100	NA	As supplemental data only	1	10
Journal of Neurosurgery: Case Lessons	The observations and lessons learned from a single case or limited case series	200	3000	5	2	45

NA = not applicable.

* Total number of words. Text = words from the Introduction through the Conclusions of the manuscript; the Abstract, Acknowledgements, References, and end matter are not included in the text total.

† Values are totals (tables + figures). JNSPG does not accept tables divided into parts (e.g., Table 1A, Table 1B, etc.); each part will be considered a separate table, and the manuscript will be returned to the author for renumbering.

‡ Indicates a structured abstract is required (headings for Objective, Methods, Results, Conclusions).

§ Applies to all article types except case reports, technical notes, and letters to the editor; use print journal limits for those.

¶ Videos may be no longer than 10 minutes in length.

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UPDATED SEPTEMBER 11, 2020

JNSPG Guidelines for Tables

Tables should be created using the table functionality tools in Microsoft Word and submitted separately from the manuscript file. We are unable to format tables imported into Microsoft Word as PICT files. We are also unable to accept tables created in spreadsheet or presentation programs (such as Excel and PowerPoint, respectively).

Tables must be cited consecutively in the text. Table parts are not allowed (e.g., Table 1A, Table 1B).

Table Formatting

- Each table should appear on its own page, with all of the tables in one Microsoft Word file.
- Each table should have a title.
- Data should be presented in a cell-based format, with the appropriate number of columns and rows.
- Do not use tabs within cells or in place of columns.
- Images, graphics, and colors (font or shading) are not permitted in tables. If these need to be included, tables should be submitted as supplemental materials.
- Abbreviations used in each table should be defined in the table footnotes.

Literature Review Tables

Tables that include references should be formatted according to the following.

- The author name (last name only, no first initial) and year should be combined into one cell. Do not put the year in a separate column.
- For 3 or more authors, "et al." should be used after the first author's name. For 2 authors, both author names should be included.
- Citation numbers must be included in superscript, to correspond with the reference included in your manuscript.

Examples of Correct Reference Styling	Examples of Incorrect Reference Styling
Cushing, 1942[8]	Cushing et. al., (1942)
Spetzler & Martin, 1986[56]	Spetzler et al, 1986[56]
Rutka et al., 2014[45]	Rutka JT(45)

Please carefully review the references in the table. Accuracy will reduce the number of reference queries you receive.

- All references in the tables must also be included in the reference section of the manuscript.
- If needed, update the citation numbering after revisions are made to the text.
- Review your references for any that were published ahead of print, and update the year of publication if needed.

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UPDATED AUGUST 13, 2020

JNSPG Guidelines for References

Please follow the *AMA Manual of Style, 11th edition*, for reference formatting (https://www.amamanualofstyle.com).

- References should be cited in the text consecutively with superscripted arabic numerals.
- References should be listed in the order in which they appear in the text.
- For all reference types, list up to six authors. If there more than six authors, list three authors, then "et al".
- Please use the NLM (PubMed) abbreviations for journal titles (https://www.ncbi.nlm.nih.gov/nlmcatalog/journals).
- An EndNote template for the AMA style is available (https://endnote.com/style_download/jama-journal-of-the-american-medical-association).

Examples

JOURNAL ARTICLES

Lacroix M, Abi-Said D, Fourney DR, et al. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. *J Neurosurg*. 2001;95(2):190-198.

JOURNAL ARTICLES ONLINE ONLY (WITH NO VOLUME OR PAGE INFORMATION)

Murray CJL. Maximizing antiretroviral therapy in developing countries: the dual challenge of efficiency and quality. *JAMA*. Published online December 1, 2014. doi:10.1001/jama.2014.16376

BOOKS & REPORTS

Cushing H, Eisenhardt L. *Meningiomas: Their Classification, Regional Behaviour, Life History, and Surgical End Results*. Charles C Thomas; 1938.

Solensky R. Drug allergy: desensitization and treatment of reactions to antibiotics and aspirin. In: Lockey P, ed. *Allergens and Allergen Immunotherapy*. 3rd ed. Marcel Dekker; 2004:585-606.

Faul M, Xu L, Wald MM, Coronado VG. *Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations, and Deaths*. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2010. Accessed June 14, 2018. https://www.cdc.gov/traumaticbraininjury/pdf/blue_book.pdf

CONFERENCE PAPERS & PRESENTATIONS

Durbin D, Kallan M, Elliott M, et al. Risk of injury to restrained children from passenger air bags. Paper presented at: 46th Annual Meeting of the Association for the Advancement for Automotive Medicine; September 20, 2002; Tempe, AZ.

MAGAZINE OR NEWSPAPER ARTICLE

Perez-Pena R. Children in shelters hit hard by asthma. *New York Times*. March 2, 2004. Accessed March 2, 2004. http://www.nytimes.com/2004/03/02/nyregion/02asthma.html

ONLINE SOURCES

AANS. About the AANS. Accessed September 19, 2019. https://www.aans.org/en/About-Us

Centers for Medicare & Medicaid Services. CMS proposals to implement certain disclosure provisions of the Affordable Care Act. December 14, 2011. Accessed April 16, 2021. https://www.cms.gov/newsroom/fact-sheets/cms-proposals-implement-certain-disclosure-provisions-affordable-care-act

For more detailed information about formatting references, please refer to the *AMA Manual of Style*.

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