Dissertation

LOW GRADE GLIOMAS TREATED AT THE UNIVERSITY OF CAPE TOWN ACADEMIC HOSPITAL COMPLEX: 2001 – 2017

by

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Declaration

I, Gisela Kahl, hereby declare that this dissertation is based on my original work, and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university. This work has not been reported or published prior to registration for the abovementioned degree.

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Abstract

LOW GRADE GLIOMAS TREATED AT THE UNIVERSITY OF CAPE TOWN ACADEMIC HOSPITAL COMPLEX: 2001 – 2017

Background: The majority of central nervous system tumours in children are low grade gliomas (LGG). Long-term survival rates are high with a slow, progressive course. Tumour location and extent of resection affect outcome. Adjuvant therapy has an important role.

Rationale: This study evaluated the demographic data of our patient population, the characteristics of LGGs in our setting, the time to presentation, and the role of adjuvant therapy including more targeted, novel biologic therapy such as BRAF/MEK inhibitors. The outcome of children with LGGs in our institution was assessed.

Methods: A retrospective analysis was performed on all children <15 years of age diagnosed with a LGG at Red Cross War Memorial Children's Hospital (RCWMCH) between 2001 and 2017. Data were collected from patient hospital folders, as well as paediatric oncology records and Groote Schuur Hospital radiotherapy records.

Results: Eighty-six children aged 0.10-13.76 years (median 4.74 years) were diagnosed with LGGs between 2001 and 2017 at RCWMCH. Median time to presentation was 60 days. Sixty-five patients (76%) were classified as having a WHO Grade I and 21 patients WHO Grade II (24%) tumours. Five patients (6%) had metastatic disease at presentation. The most common sites involved were the cerebellum (27%), hypothalamus (17%) and cerebrum (14%). The most common histology was juvenile pilocytic astrocytoma (JPA) (n=62; 73%). Gross total resection (GTR) was achieved in 21 patients (24%). Twenty-four patients (27%) received chemotherapy of which 11 patients progressed. Twenty-two patients received radiotherapy (26%), of which 3 patients progressed. The estimated 5-year overall survival (OS) was 86.8% and the estimated 5-year progression free survival (PFS) was 42.8%. The presence of a $BRAF^{V600E}$ mutation was checked in 4 patients since 2013, all had JPA histology, and all were negative.

Discussion: Our patient demographic differed from published data with respect to younger age at presentation and female predominance. Time to presentation was relatively short. The majority of LGGs were cerebellar, with JPA histology being the most common. GTR was achieved in almost a quarter of patients. WHO Grade II histology did not significantly impact PFS and OS. Children <3 years had a lower PFS compared to children > 3 years, but OS was

similar. OS in this study was comparable to published data in developed countries, however PFS was slightly lower.

Conclusion: Our outcomes are similar to those achieved in developed countries. Chemotherapy and radiotherapy are valuable adjuncts to treatment. The presence of a BRAF alterations should be tested in recurrent/progressive disease, to guide use of novel treatments.

Acknowledgements

I would like to thank my supervisor, Professor Alan Davidson, for his continued support and assistance in this research study.

Tables

Table 1. The 2016 WHO Classification of CNS Tumours

ASTROCYTIC TUMOURS	**Grade I**	**Grade II**	**Grade III**	**Grade IV**
Subependymal Giant Cell Astrocytoma (SEGA)	•			
Pilocytic Astrocytoma	•			
Pilomyxoid Astrocytoma	Not officially graded			
Diffuse Astrocytoma		•		
Pleomorphic Xanthoastrocytoma		•		
Anaplastic Astrocytoma			•	
Glioblastoma				•
Gliosarcoma				•
OLIGODENDROGLIAL TUMOURS				
Oligodendroglioma		•		
Anaplastic Oligodendroglioma			•	
OLIGOASTROCYTIC TUMOURS				
Oligoastrocytoma		•		
Anaplastic Oligoastrocytoma			•	

Table 2. Patient demographics

Category		**Number (%)**
Gender		
Male		40 (47)
Female		46 (53)
Location		
Infratentorial		38 (44)
Supratentorial		48 (56)
Grade (all histologies)		
Grade I		66 (77)
Grade II		20 (23)
Histology		
Juvenile Pilocytic Astrocytoma		63 (73)
Diffuse Astrocytoma		10 (12)
Pilomyxoid Astrocytoma		6 (7)
Subependymal Giant Astrocytoma		3 (4)
Neuronal tumours		2 (2)
Pleomorphic xanthoastrocytoma		2 (2)
Extent of resection		
Gross Total Resection		21 (24)
Subtotal resection		22 (26)
Biopsy only		30 (35)
No surgery		13 (15)
Neurocutaneous Syndromes		
	Neurofibromatosis 1	9 (11)
	Tuberous Sclerosis Complex	3 (4)
Radiation		
No radiation therapy		64 (74)
Radiation therapy		22 (26)
	First line treatment	6
	Second line treatment	7
	Third line treatment	9
Chemotherapy		
No chemotherapy		62 (72)
Chemotherapy		24 (28)
	First line treatment	16
	Second line treatment	9
	Third line treatment	7

Figures

Figure 1. Age distribution at presentation

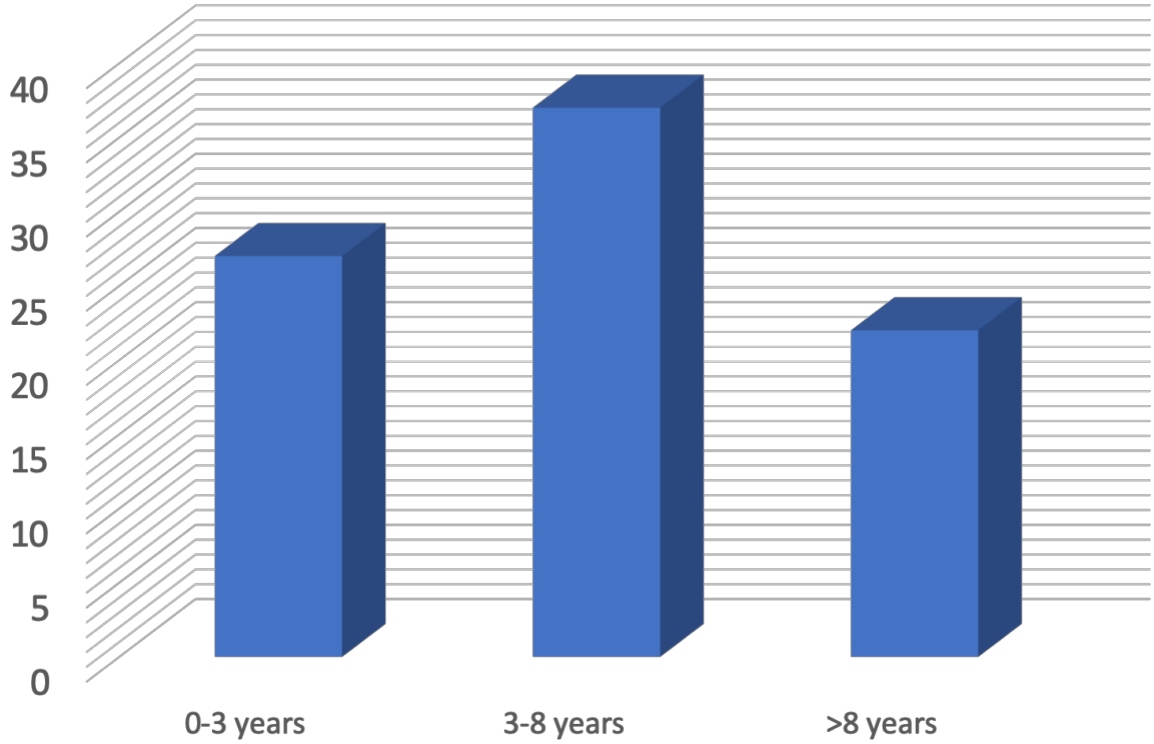


Figure 2. Sites of involvement

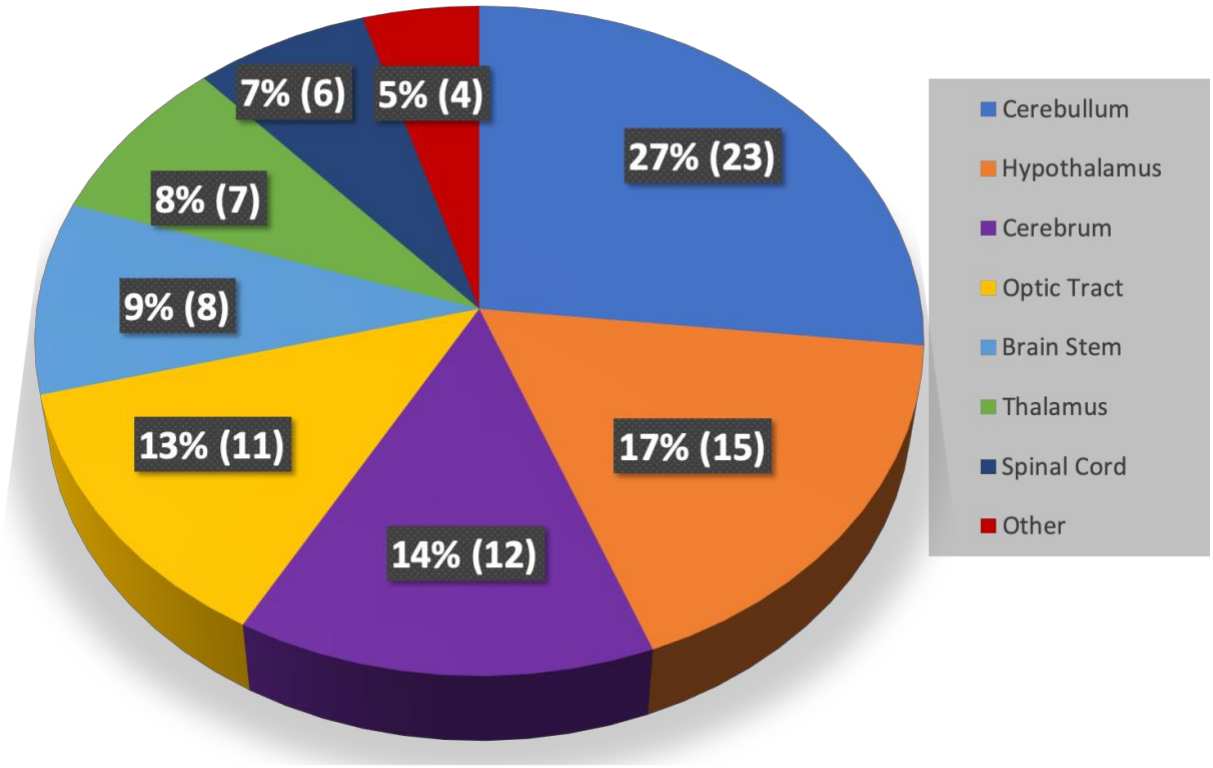


Figure 3. Estimated 5-year OS according to WHO Grade

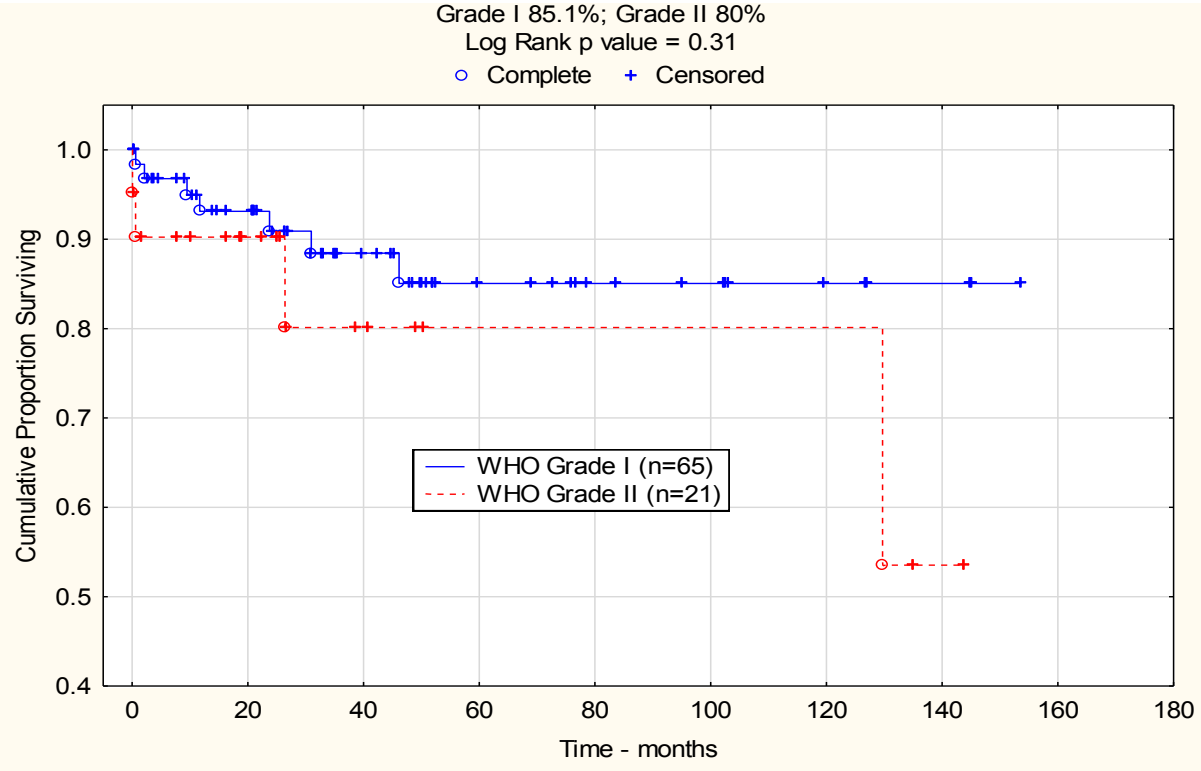
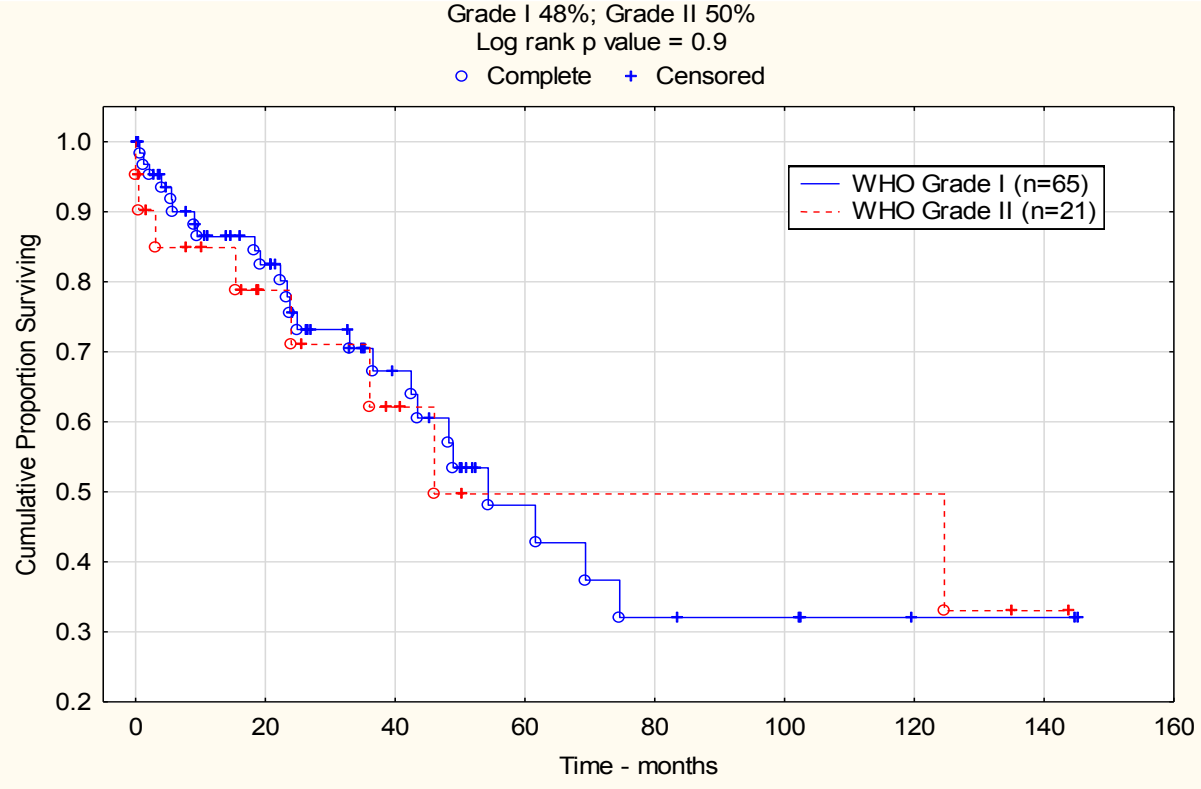


Figure 4. Estimated 5-year PFS according to WHO Grade



List of abbreviations

BRAF	B-raf kinase
EFS	Event free survival
ETV	Endoscopic third ventriculostomy
EVD	External ventricular drain
FGFR1	Fibroblast growth factor receptor 1
GSH	Groote Schuur Hospital
GTR	Gross total resection
JPA	Juvenile pilocytic astrocytoma
LGG/LGGs	Low grade glioma/Low grade gliomas
MAPK	Mitogen-activated protein kinase
MEK	MAPK/ERK kinase
MRI	Magnetic resonance imaging
NF1	Neurofibromatosis 1
NTRK	Neurotrophic tropomyosin receptor kinase
OS	Overall survival
PFS	Progression free survival
RCWMCH	Red Cross War Memorial Children's Hospital
SEGA	Subependymal giant cell astrocytoma
TSC	Tuberous sclerosis complex
VC	Vincristine and carboplatin
VPS	Ventriculoperitoneal shunt
WHO	World Health Organisation

Chapter 1 - Introduction

Context

Central nervous system tumours are the most common solid tumours in children, and of these, the majority are low grade gliomas (LGGs) (1). LGGs arise from the supporting glial cells of the central nervous system, and as such can arise from any structure within the neuroaxis, including the cerebellum, cerebral hemispheres, deep midline structures, optic pathway, spinal cord and brainstem. Glial cells are either astrocytes, oligodendrocytes, or ependymal cells. These cells support neuronal function, myelinate axons and contribute to the cerebrospinal fluid brain barrier in the ventricles (1).

The 2016 World Health Organization (WHO) Classification of Tumours of the Central Nervous System is an updated version of the 4th edition from 2007. While the tumour classifications are still based on the cell of origin or anatomical origin, novel molecular characteristics have been incorporated into this new classification system (2). This classification system assigns neoplasms with moderate cellularity and few or no histologic features of malignancy as low grade, or Grade I and Grade II lesions (1). Broad classification groups include astrocytic, oligodendroglial, and oligoastrocytic tumours (see Table 1). Long-term survival rates are high, with a slow, progressive course, which is characteristic of LGGs (1).

The most common type of paediatric LGGs is pilocytic astrocytoma (1). These tumours have distinct histological and biological characteristics, are typically slow growing, and may even regress spontaneously (3). Supratentorial LGGs, which describes tumours in the cerebral hemispheres, basal ganglia, thalamic nuclei, lateral ventricles, hypothalamus and corpus collosum, are considered to have poorer outcomes compared with LGGs in other locations. In addition to tumour location, patient age and extent of resection remain the most important prognostic indicators (4). Malignant transformation as well as dissemination in this group of LGGs on presentation in the paediatric population is reported to be low (5).

In contrast to most adult gliomas, up to 10% of paediatric gliomas arise in association with inherited germline mutations, specifically Tuberous Sclerosis Complex (TSC), and Neurofibromatosis 1 (NF1) (6). NF1 is inherited in an autosomal dominant fashion and is associated with a predisposition to the development of pilocytic astrocytomas of the entire optic pathway and hypothalamus, as well as diffuse astrocytomas. Patients with tuberous

sclerosis have a predisposition to subependymal giant cell astrocytomas (SEGA), which arise in the ventricles. Prognosis and treatment options for children who do carry a genetic mutation is often very different from a child with the same type of tumour without a genetic mutation. For example, children with NF1 and optic pathway/hypothalamic gliomas often have very good progression free survival (PFS) and lower risk of visual problems. On the other hand, their risk of radiotherapy-related morbidity can be very high, and some chemotherapeutic agents need to be avoided altogether in view of high risk of adverse effects, such as second malignancies with alkylating agents (7).

Presenting symptoms of LGGs include generalising and localising symptoms. Generalising symptoms such as headaches, nausea and vomiting and lethargy are caused by raised intracranial pressure, whereas localising signs depend on the tumour location, including focal neurological findings, seizures, and endocrinopathies. Signs elicited during physical examination range from isolated nerve palsies, decreased visual acuity, proptosis and strabismus, to long tract signs including hemiparesis, spasticity and hyperreflexia (7).

Treatment options include surgical resection, chemotherapy, radiotherapy, or a combination of these. In addition, for a certain group of patients, expectant observation is preferred (7). These include patients with typical optic pathway/hypothalamic gliomas, especially in children with NF1, with non-progressive tumours in deep midline structures or the brain stem, where surgery would cause significant morbidity (7). Complete surgical resection, where feasible, is the treatment of choice as it may be curative, with the best chance of prolonged progression free survival (PFS) (8). However, if only subtotal or incomplete resection is possible, the risk of progression or relapse is substantial.

Established chemotherapy options include vincristine and carboplatin (9), or a combination of thioguanine, procarbazine, lomustine, vincristine (TPCV) (10). Five-year event free survival (EFS) is around 45% for both chemotherapy regimens (11). Single agent vinblastine has shown promising results for patients with progressive, unresectable LGGs (12), as has temozolomide (13). Other treatment options in refractory or progressive disease include bevacizumab and irinotecan (14).

Radiotherapy has a great role to play in patients with progressive or recurrent disease, or tumours that are inoperable at diagnosis (15,16). In appropriately selected patients, radiotherapy is more definitive than chemotherapy, with a 5-year EFS of 74.3% and OS of 98.5% (17). However, radiotherapy significantly increases long term morbidity, with an

increased risk of second malignancies, significant neurological problems, such as seizures, blindness, coordination problems and endocrine problems such as growth failure, obesity and hypothyroidism (18).

Targeted therapy has developed rapidly over the last few years. The aim is to improve tumour control with the least side effects, resulting in better quality of life. One example is the use of mTOR inhibitors for Subependymal Giant Cell Astrocytomas (SEGA) associated with Tuberous Sclerosis (19). Although LGGs in children represent a heterogeneous group of tumours, the majority of them involve the mitogen-activated protein kinase (MAPK) pathway. Mutations of the BRAF gene, which is part of the MAPK pathway, leads to cell cycle dysfunction. $BRAF^{V600E}$ mutations (point mutation leading to a valine to glutamate substitution at position 600) are found in varying degrees in the different subtypes of LGGs. For instance, they are found in 60-80% of pleomorphic xanthoastrocytomas, but only 5-10% of pilocytic astrocytomas. The presence of the mutation is associated with poorer response to conventional chemotherapy and poorer overall survival (20). Numerous clinical trials are investigating BRAF inhibitors (vemurafenib (21) and dabrafenib (22)), as they allow for targeted molecular therapy (23). As this is a single pathway disease, patients who fail first and second line strategies, and are either $BRAF^{V600E}$ negative or not responsive to BRAF inhibitors, should respond to MEK-1 inhibitors such as trametinib (24) and selumetinib (25), and drug trials are under way to explore these agents.

Long term overall survival amongst children with LGG is at least 83% in developed countries, even with incomplete tumour excision. There is a significant difference in overall survival however, between Gr I and II LGGs, with 5-year OS of approximately 96% for pilocytic astrocytoma (Gr I) and 48% for diffuse astrocytoma (Gr II) (26). Amongst long-term survivors of LGGs, significant morbidity is experienced by many, including adverse neurocognitive effects, blindness, deafness, and serious endocrine sequelae (18). However, a study looking specifically at quality of life in children with LGGs found that, despite tumour and/or treatment associated morbidity, children rated their quality of life higher than that of their peers (27). There is also a low likelihood of paediatric LGG-related death in adult survivors, the greatest risk being associated with radiation exposure at a young age. It is thus important to minimize treatment-associated morbidity, especially related to radiotherapy (28).

There is little recent data available with regards to paediatric LGGs in South Africa, as well as in developing countries as a whole. A retrospective study performed in Egypt showed

similar patient demographics, clinical presentation, location and pathology of paediatric LGGs compared to developed countries. However, it showed a lower incidence of LGGs (16.9 per million per year) compared to developed countries (29.9 in Europe) (29). This is most likely due to an underestimation as a result of underreporting or lack of detection and not due to actual lower incidence (30). A retrospective study done in Nigeria also showed similar demographics and presenting signs to those in developed countries. However, late presentation (mean interval 13.4 months) was significantly higher compared to that in developed countries, such as Canada (7.3 months) (31) (32). Reasons mentioned for this may be the emphasis on traditional medicine, low levels of education of caregivers, and a higher rate of poverty. In addition, this study showed low survival rates of 56% and 47% at 1 and 5 years, respectively (31). Little attention was paid to brain tumours at South African conferences before the advent of the Paediatric Brain Tumour Workshops in the first decade of the new millennium (33).

Children with LGGs receive multidisciplinary care at Red Cross Children's Hospital and Groote Schuur Hospital, which forms part of the University of Cape Town's academic complex. Multidisciplinary care involves the departments of neurosurgery, radiation oncology, paediatric oncology, pathology and radiology, with input from an educational psychologist, occupational therapist and social worker. Integrated care for children with brain tumours has had a great impact on patients and their long term follow up (33).

The aim of this study was to analyse the demographics, disease characteristics, time to presentation and management of children with LGGs and determine outcomes, specifically looking at and comparing outcomes to other developing countries. Demographic data was compared to published data, including tumour location and histology. BRAF status has been tested in some patients in our institution since 2013. The number of patients tested, the results thereof, and implications for future management are discussed.

Ethical considerations

This is a retrospective study, therefore informed consent from each patient is deemed unnecessary. Patient data is gathered from their patient files which are locked in the Paediatric Oncology Department at Red Cross Children’s Hospital. The patient data is stored in the department’s computer system, which is password protected. Patient confidentiality will be maintained, as patients’ data are assigned numbers in the database,

thus keeping patient's data anonymous. Patient names and details will not be published or used in any form of presentation. The principles of beneficience/non-malificience were followed in this study.

This study will serve as a dissertation for an MPhil project and will be put forward for a publication in a peer review journal.

Ethics approval was obtained from the University of Cape Town's Faculty of Health Science's Human Research Ethic Committee (Ethics reference number: HREC REF 340/2018) (Appendix 3).

Journal for Publication

The Journal of Pediatric Hematology/Oncology (JPHO) is the journal selected for publication. JPHO has an impact factor of 1.076. JPHO has a wide readership and publishes relevant research articles pertaining to childhood oncology and haematology. JPHO is listed on the South African Department of High Education's list of accredited journals. The publication-ready manuscript has been formatted according to the JPHO author guidelines (Appendix 4).

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Chapter 2 - Publication ready manuscript

LOW GRADE GLIOMAS TREATED AT THE UNIVERSITY OF CAPE TOWN ACADEMIC HOSPITAL COMPLEX: 2001-2017

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Background

The majority of central nervous system tumours in children are low grade gliomas (LGGs). Long-term survival rates are high, with tumour location and extent of resection affecting outcome. Adjuvant therapy has an important role. This study evaluated the characteristics and outcome of children with LGG.

Procedure

A retrospective analysis was performed on all children <15 years diagnosed with LGGs at Red Cross War Memorial Children's Hospital and Groote Schuur Hospital between 2001 and 2017. Data were collected from patient hospital folders.

Results

Eighty-six children aged 0.10-13.76 years (median 4.74 years) were included. Median time to presentation was 60 days. WHO Grade I gliomas were more common (n=66;77%) than Grade II tumours (n=20;23%). The most common sites were the cerebellum and hypothalamus. Twenty-one patients (24%) had a complete resection. Twenty-four patients (28%) received chemotherapy. Twenty-two patients received radiotherapy (26%), 3 patients progressed.

$BRAF^{V600E}$ mutation was tested for in 4 patients, all were negative. The estimated 5-year Overall Survival (OS) was 86.8%, the estimated 5-year Progression Free Survival (PFS) was 42.8%.

Conclusions

Our outcomes are similar to those achieved in developed countries. Chemotherapy and radiotherapy are valuable adjuncts to treatment. BRAF alterations should be tested for in recurrent/progressive tumours to guide choice of novel agents.

Key words: low-grade glioma, paediatric, chemotherapy, radiotherapy

Introduction

Central nervous system tumours are the most common solid tumours in children, and of these, the biggest single group are low grade gliomas (LGGs). They comprise a heterogenous group of tumours with different histologic subtypes, clinical behaviour, location and biology. Tumour location, patient age, and extent of resection are the most important prognostic indicators.[1,2] Children with diencephalic syndrome and hypothalamic tumours have the poorest overall survival.[3]

The majority of LGGs arise spontaneously. However, two cancer-predisposition syndromes, neurofibromatosis type 1 (NF1) and tuberous sclerosis complex (TSC), are associated with an increased frequency of pilocytic astrocytomas and subependymal giant cell astrocytomas (SEGAs), respectively.[1]

Gross total resection (GTR) provides excellent long-term survival;[4] however, progression frequently occurs in incompletely resected tumours and may necessitate adjuvant therapies, including chemotherapy, radiotherapy or further surgery. Some LGGs are considered irresectable, such as hypothalamic or chiasmic tumours – they present in young children, and can impact on vision and can cause endocrine dysfunction.[3]

Chemotherapy was first introduced as a form of treatment for LGGs in the 1970s.[5] Its use was aimed at delaying the need for radiotherapy to minimise the adverse cognitive, endocrine and vascular consequences.[3] Vincristine and carboplatin (VC) is standard first line chemotherapy, with an over 90% non-progression rate at 24 weeks for patients with newly diagnosed disease or those with progression. Etoposide in addition to VC has not shown to improve PFS or OS.[3] Other treatment options include a combination of thioguanine, procarbazine, lomustine and vincristine (TPCV),[6] single agent vinblastine,[7] vinorelbine,[8] temozolomide[9] and bevacizumab, with or without irinotecan.[10-13]

Radiotherapy is reserved for those with progressive or recurrent disease.[14-15] In those patients where GTR is not possible, PFS is improved with radiotherapy.[16-17] In fact, some studies have shown that patients undergoing subtotal resection or biopsy only who receive postoperative radiotherapy achieve similar rates of OS compared to those where GTR was achieved.[18] Radiotherapy may be a definitive way to treat disease that is no longer chemo-sensitive in a patient group where surgery carries significant morbidity and risk to function.[14] The concern

is late toxicity from ionising radiation causing adverse neuro-cognitive effects and hypopituitarism.[17] Depending on the exact location of the tumour and the organs at risk close to or in the target area, other organs such as the lens and inner ear can also be affected, causing functional deficits at a later stage.[17] The current accepted radiotherapy dose is 50.4-54Gy.[14] Radiotherapy has evolved rapidly in the last few decades, with the development of highly conformal and precise planning techniques using cross-sectional imaging for contouring and MRI fusion for better visualisation. The ability to control the tumour and spare normal tissue is improving.[14]

Targeted therapy research has developed rapidly over the last few years. All LGGs harbor an alteration in the MAPK axis, including BRAF fusion (*KIAA1549:BRAF* fusion) and mutation ($BRAF^{V600E}$), and RAF1 fusions and mutations involving the FGFR1 and NTRK genes.[19] BRAF fusions are almost exclusive to pilocytic astrocytomas, whereas $BRAF^{V600E}$ mutations are seen mostly in pleomorphic xanthoastrocytomas and gangliogliomas. Recent Phase II trials using agents that block MEK 1/2 (MAPK/ERK kinase) have shown promising results, and further studies will be done incorporating these agents with standard chemotherapy agents.[16,20]

Long term overall survival amongst children with LGGs is at least 83% in developed countries, even with incomplete tumour excision.[2] Among long-term survivors of LGGs, significant morbidity is experienced by many, including adverse neurocognitive effects, blindness, deafness, and serious endocrine sequelae.[17]

There is little recent data available with regards to paediatric LGGs in South Africa. The aim of this study was to analyse the demographic data of our patients, our management of children with LGGs and to determine outcomes, specifically looking at and comparing outcomes to other developing countries. The presence of BRAF mutations were tested in some patients since 2013 – the results of these were evaluated.

Materials and Methods

This was a retrospective analysis of all patients between 0-15 years treated for LGGs at Red Cross War Memorial Children's Hospital (RCWMCH) and/or Groote Schuur Hospital (GSH) between January 2001 and December 2017. These are academic referral hospitals which form part of the University of Cape Town's academic complex. Both hospitals treat patients from the Eastern and Western Cape provinces.

RCWMCH's paediatric oncology unit sees approximately 130 new patients each year, of which a third are brain tumours. Multidisciplinary care offered to children with brain tumours include neurosurgery, radiology, oncology, pathology, with input from educational psychologists, occupational therapists, physiotherapists, dieticians and social workers. These services are provided at RCWMCH. Radiation oncology is provided to both adults and children at GSH.

Ethics approval was obtained from the University of Cape Town's Faculty of Health Science's Human Research Ethic Committee (Ethics reference number: HREC REF 340/2018) (Appendix 3) prior to commencing the retrospective review. Data was collected from patient folders at RCWMCH and GSH and were entered onto a *Microsoft Access*^{TM} database (Appendix 2), which was password protected. Two patient folders could not be found and these patients were thus excluded from the study. Descriptive analysis was performed using *Excel*^{TM}. Included in the datasheet are patient details, histology, metastases, symptoms and signs, type and details of treatment received, BRAF status (if applicable), and time from initial symptoms to diagnosis. *Statistica*^{TM} was used to analyse treatment outcomes and PFS was represented on Kaplan-Meier curves. Statistical significance was defined as $P \leq .05$.

All children had a magnetic resonance imaging (MRI) of the brain and spine at diagnosis - this was either done at the referring hospital or at RCWMCH. Diagnosis of a LGG was either made by imaging alone or with histology. If the location of the mass was in the optic nerve/chiasm, a biopsy was not performed, and the diagnosis was made on imaging alone. Metastatic disease was defined as either spinal involvement on imaging, and/or positive cerebrospinal fluid.

Time to presentation was defined as the interval from symptom onset to the first imaging report. Symptom duration was based on the patient's or family's report in the initial history taking.

Symptom duration was recorded in days. If the child presented with multiple symptoms, the symptom with the longest duration was used in the analysis.

Appropriate management is determined on a patient by patient basis as a multidisciplinary discussion with the paediatric oncology, neurosurgery, pathology, radiology and radiation oncology teams. Long term follow up and surveillance is provided at a combined monthly clinic, which is also attended by paediatric endocrinologists, an educational psychologist, and an occupational therapist.

Masses deemed resectable upfront on imaging were removed as far as possible. Gross total resection (GTR) was attempted for cerebellar and cerebral hemisphere lesions, with biopsy or debulking resection for tumours in other sites. Second surgery was performed either if a biopsy was needed to confirm diagnosis, or if total resection was deemed feasible after neoadjuvant chemotherapy or radiotherapy. $BRAF^{V600E}$ mutation testing on immunohistochemistry was done in those not responding to chemotherapy, where targeted therapy would perhaps be a potential treatment. Testing of BRAF fusion is currently not feasible

Patients presenting with hydrocephalus either had an extraventricular drain (EVD), endoscopic third ventriculoscopy (ETV), or ventriculoperitoneal shunt (VPS) placed, at the discretion of the treating neurosurgeon. Cerebrospinal fluid was sampled when deemed necessary to exclude metastatic disease.

Children less than 8 years old were either started on chemotherapy or followed a watch and wait approach, in an attempt to delay or avoid radiotherapy entirely. Standard chemotherapy consisted of vincristine and carboplatin, based on SIOP LGG 2003.[3] Radiological, clinical and ophthalmological response assessment was scheduled at week 10, 24 and 54 weeks. If the patient progressed on first line chemotherapy, or if the patient developed a carboplatin hypersensitivity, the patient was started on vinblastine, which is second line chemotherapy. Third line chemotherapy is bevacizumab and irinotecan.

Radiotherapy was used as primary treatment for patients older than 8 years according to the local protocol, and where indicated by poor response in younger patients. However, in the latter group, radiotherapy was deferred for as long as possible to avoid adverse neurocognitive effects. All patients received fully fractionated photon radiotherapy. The treatments given were

a mixture of 3D conformal radiotherapy with static fields and dynamic and volumetric modulated arc therapy in more recent years. Children requiring sedation were sedated with oral alimemazine and droperidol in earlier years and later, with intravenous dexmedetomidine.

At relapse or progression, consideration was given to surgery in the first instance. Tumours not amenable to surgery in younger children under the age of 8 years received chemotherapy, and older children were treated with radiotherapy. Only those patients with disease progression below radiotherapy age requiring third line chemotherapy were tested for the $BRAF^{V600E}$ mutation on immunohistochemistry, in order to establish whether a BRAF inhibitor should be used in place of or in combination with a MEK inhibitor. Currently, BRAF fusion testing is not available locally. $BRAF^{V600E}$ testing only recently became available, and as such testing was done prospectively in those patients with disease progression below radiotherapy age requiring third line chemotherapy. A retrospective immunohistochemical analysis on samples could be the objective of a separate study in the future.

Results

Eighty-six children were included in the study. Males comprised 47% (40/86) and females 53% (46/86). Ages ranged from 0.10 to 13.76 years with a median age of 4.74 years (see Table 2). The median time from onset of symptoms to diagnosis was 60 days. The mean number of days was 108 days with a standard deviation of 278 days. This finding was due to one outlier with a time to presentation of 4 years.

Sixty-six patients (77%) had LGGs classified as WHO Grade I, and 20 patients classified as WHO Grade II (23%). The histologies included JPA in 63 patients (73%), diffuse astrocytoma in 10 patients (12%), pilomyxoid astrocytoma in 6 (7%), SEGA in 3 (4%), neuronal tumours in 2 patients (2%), and pleomorphic xanthoastrocytomas in 2 patients (2%) (Table 2).

The sites involved were the cerebellum in 23 patients (27%), hypothalamus in 15 patients (17%), cerebrum in 12 patients (14%), optic tract in 11 patients (13%), 8 patients had a LGG in the brainstem (9%), 7 patients in the thalamus (8%), 6 patients (7%) in the spine, and 4 patients in other locations (1 patient in the pineal gland, 3 patients in the intraventricular system; 5%) (see Figure 1). Thirty-eight patients (44%) had LGGs in an infratentorial location, and 48 (56%) patients had a supratentorial LGG. Five patients (6%) had metastatic disease at presentation. Two patients had hypothalamic, 2 had cerebral and 1 patient had a brainstem LGG. Twelve patients had a neurocutaneous syndrome – nine patients (10%) had NF1, and 3 patients (3%) had TSC (Table 2). Of the patients who had NF1, 4 patients had a JPA, and 5 patients had optic gliomas. For 6 patients, a watch and wait approach was adopted, and 2 patients received chemotherapy. One patient had debulking surgery at diagnosis, and then again at progression. In the 3 patients with TSC and SEGA, one patient's tumour was completely resected, the second patient was operated twice but died as a result of a VPS infection. The third patient was lost to follow up.

Of the 86 patients, 30 patients (35%) had a biopsy only, 22 (26%) had debulking surgery, and 21 (24%) patients had a gross total resection. Thirteen patients (15%) had no form of surgery - the diagnosis was based on unequivocal neuroradiological appearance. All 52 patients (60.5%) with hydrocephalus had a shunt inserted, and these were revised when necessary.

Twenty-four patients (27%) received chemotherapy. Sixteen patients received chemotherapy as first line treatment, 9 patients as second-line treatment, and 7 patients as third-line treatment. All but two patients received vincristine and carboplatin as first line chemotherapy (Table 2).

Twenty-two patients received radiotherapy (26%). Six patients received radiotherapy as first line treatment, 7 patients received radiotherapy as second line treatment, and 9 patients as third line treatment (Table 2). Three patients progressed after radiotherapy. Crude PFS was 86.4% in this group.

The estimated 5-year Overall Survival (OS) for the whole group was 86.8% and the estimated 5-year Progression Free Survival (PFS) was 42.8%. Estimated 5-year OS and EFS for those receiving chemotherapy was 95.6% (86.4% at 62 months) and 35.8% respectively. Estimated 5-year OS was 85.1% for WHO grade I tumours and 80% for WHO grade II tumours (Log rank p value 0.31) (see Figure 3), and estimated 5-year PFS was 48% for WHO grade I tumours and 50% for WHO grade II tumours (Log rank p value 0.9) (see Figure 4). Estimated 5-year OS was 79.5% for children under 3 years and 86.8% for children over three years (Log rank p value 0.39), but estimated 5-year PFS was 34.7% for children under the age of 3 years and 57.6% for those above 3 years (Log rank p value 0.03)

$BRAF^{V600E}$ mutation testing was performed on immunohistochemistry in 4 patients, all of which were negative. All 4 patients had a diagnosis of a JPA.

Discussion

This study is the first analysis of paediatric patients with LGGs in South Africa. This study showed a greater number of females than males, in contrast to other studies, where there was a male predominance.[2,3,18,21,22] The median age at presentation was 4.74 years, which is lower compared to other studies.[2,22,23] Pilocytic astrocytoma was the most common type, consistent with other studies.[2,4,18]

In this study, the most common sites involved were the cerebellum and hypothalamus, which was in keeping with findings in other studies.[2] Supratentorial LGGs were more common than infratentorial tumours, comparable to published data.[2] It is estimated that approximately 5% of children with LGGs present with leptomeningeal dissemination,[24] which was not significantly different in this study, where 6% of patients had metastatic disease at presentation.

Pre-diagnosis symptom interval is a very subjective measurement. The median time from onset of symptoms to presentation to a health facility in this study was 60 days, which was short compared to other studies in both developed and developing countries, with a median range of 2 – 14 months.[25-27] Certainly it is encouraging to compare our experience with the detailed data that emerged from the very successful HEADSMART campaign in the United Kingdom where the median time to diagnosis interval for brain tumours fell from 14 weeks in 2004-6 to 6.7 weeks in 2013.[28] We have to concede that the short symptom duration may be due to underreporting by the caregiver. Delayed diagnosis in a low/middle income country highlights challenges related to access to care, cultural influences such as emphasis on traditional medicine, low levels of education of parents and caregivers, and poverty.[29] Other possible factors contributing to the delayed diagnosis are children's ability to adjust to and accommodate slow-growing tumours like LGGs. With subtle neurological deficits that may be difficult to recognize, and very young children being unable to voice complaints such as headaches or visual compromise.[26-27] The impact of these delays is an area of controversy. A large study looking at pre-diagnosis symptom interval did not show a significant impact on negative outcomes, most likely due to the insidious nature of LGGs. The duration of symptoms was also not significantly associated with achieving GTR.[21] But a study conducted at St Jude did show inferior neurocognitive outcomes for those children with a delay of more than 3 months.[30]

LGGs in childhood are associated with excellent long-term survival rates, with a low likelihood of LGG related death in adult survivors. Treatment strategies with the aim of minimising long-term effects for children with LGGs during childhood thus need to carefully considered.[2] Extent of tumour resection is strongly associated with better OS and PFS,[4] however, GTR needs to be carefully weighed against long-term morbidity post resection. GTR was accomplished in 24% of patients in this study, which is slightly lower than the GTR rate of 27% attained in a large review in the United States of America.[31]

When GTR is not achieved upfront, adjuvant radiotherapy is known to drastically improve PFS but not OS.[32] In this study, 26% of patients received radiotherapy, which is slightly higher than reports from other centers.[2,32] This is probably due to the local policy making radiotherapy the primary treatment in children over 8 years with irresectable tumours. Only 3 patients progressed after radiotherapy, confirming its important role as an adjuvant therapy. Long-term morbidity following radiotherapy is not limited to young children and needs to be considered carefully. Adverse neurocognitive effects on intelligence quotient, memory, and attention may necessitate remedial education for the child.[23]

Our 5-year OS of 86.8% was comparable to those achieved in other centers.[21] This is in stark contrast to other studies in developing countries, which showed low survival rates of 56% and 47% at 1 and 5 years, respectively.[29] Our 5-year PFS was slightly lower at 42.8% compared to other studies.[21] This may be due to slightly lower GTR rates. This study showed no significant difference in PFS or OS for those with Gr I vs Gr II histology. There have been mixed findings in the literature, some which found a significant difference in overall survival,[21,31] others which did not.[25] Estimated 5-year PFS for children over 3 years was significantly higher than for children under 3 years of age, a finding supported by other studies.[1,31]

The presence of the BRAF ^{V600E} mutation was tested in only a small number of patients, after poor response or progression on second line chemotherapy. All of these patients had JPAs, only a small percentage of which are known to harbor BRAF^{V600E} mutations.[33] One of these patients has subsequently been commenced on the MEK1 inhibitor Trametinib, with good response. The good response was most likely due to it being a BRAF fusion positive tumour, rather than due to a lack of a positive BRAF^{V600E} mutation. Although these novel agents have shown good response rates and good PFS with overall low toxicity profiles, there are a number of questions that have as yet not been answered. These include the appropriate duration of

therapy, especially in view of late toxicities with chronic administration, and durability of response once therapy is stopped.[34]

The following limitations need to be taken into account. It needs to be taken into consideration that interpreting retrospective data many years later, with changes in diagnostics, therapies and referral patterns may have introduced bias to the results. The quality of the data extracted depends on how it is entered into the database. Bias may have been introduced during this process, as it was done by different investigators.

Conclusion

This study in children with LGGs shows similar OS to those in developed countries, with a slightly lower PFS. Radiotherapy and chemotherapy are valuable adjuncts to surgical resection. Multidisciplinary care is paramount in this group of children, and long-term effects following treatment need to be carefully considered. $BRAF^{V600E}$ alterations should be tested in a selected cohort of patients in the setting of progression/recurrence, where targeted therapy could be of benefit.

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Appendices

Appendix 1: Research protocol

Research Protocol

Low grade gliomas treated at the UCT academic hospital complex: 2001-2017

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Background

Central nervous system tumours are the most common solid tumours in children, and of these, the majority are low grade gliomas (LGG) (1). LGG arise from the supporting glial cells of the central nervous system, and as such can arise from any structure within the neuroaxis, including the cerebellum, cerebral hemispheres, deep midline structures, optic pathway, spinal cord and brainstem. Glial cells are either astrocytes, oligodendrites, or ependymal cells. These cells support neuronal function, myelinate axons and contribute to the cerebrospinal fluid brain barrier in the ventricles.

The 2016 World Health Organization (WHO) Classification of Tumours of the Central Nervous System is an updated version of the 4th edition from 2007. While the tumour classifications are still based on the cell of origin or anatomical origin, novel molecular characteristics have been incorporated into this new classification system (2). This classification system assigns neoplasms with moderate cellularity and few or no histologic features of malignancy as low grade, or grade I and grade II lesions (1). Broad classification groups include astrocytic, oligodendroglial, and oligoastrocytic tumours (see table). Long-term survival rates are high, with a slow, progressive course, which is characteristic of LGG.

ASTROCYTIC TUMOURS	Grade I	Grade II	Grade III	Grade IV
Subependymal Giant Cell Astrocytoma (SEGA)	•			
Pilocytic Astrocytoma	•			
Pilomyxoid Astrocytoma	Not officially graded			
Diffuse Astrocytoma		•		
Pleomorphic Xanthoastrocytoma		•		
Anaplastic Astrocytoma			•	
Glioblastoma				•
Gliosarcoma				•
OLIGODENDROGLIAL TUMOURS				
Oligodendroglioma		•		
Anaplastic Oligodendroglioma			•	
OLIGOASTROCYTIC TUMOURS				
Oligoastrocytoma		•		
Anaplastic Oligoastrocytoma			•	

The 2016 WHO Classification of CNS Tumours

The most common type of paediatric LGG is pilocytic astrocytoma (1). These subtypes of tumours have distinct histological and biological characteristics, are typically slow growing, and may even regress spontaneously (3). Supratentorial LGG, which describes tumours in the cerebral hemispheres, basal ganglia, thalamic nuclei, lateral ventricles, hypothalamus and corpus collosum, are considered to have poorer outcomes compared with LGG in other locations. In addition to tumour location, patient age and extent of resection remain the most important prognostic indicators (4). Malignant transformation as well as dissemination in this group of LGG on presentation in the paediatric population is reported to be low (5).

In contrast to most adult gliomas, up to 10% of paediatric gliomas arise in association with inherited germline mutations, specifically TSC1 or TSC2 (Tuberous Sclerosis

complex), and NF1 (Neurofibromatosis 1) (6). NF1 is inherited in an autosomal, dominant fashion, and is associated with a predisposition to the development of pilocytic astrocytomas of the optic nerve and chiasm, as well as diffuse astrocytomas. Tuberous sclerosis is associated with subependymal giant cell astrocytoma (SEGA), and arises from the ventricles. Prognosis and treatment options for children who do carry a genetic mutation is often very different from a child with the same type of tumour without a genetic mutation. For example, children with NF1 and optic pathway/hypothalamic gliomas often have favourable progression free survival (PFS) and lower risk of visual problems. On the other hand, their risk of radiotherapy-related morbidity can be very high, and some chemotherapeutic agents need to be avoided altogether in view of high risk of adverse effects (7).

Presenting symptoms of LGG include generalizing and localizing symptoms. Generalising symptoms such as headaches, nausea and vomiting and lethargy are caused by raised intracranial pressure, whereas localizing signs depend on the tumour location, including focal neurological findings, seizures, and endocrinopathies. Signs elicited during physical examination range from isolated nerve palsies, decreased visual acuity, proptosis and strabismus, to long tract signs including hemiparesis, spasticity and hyperreflexia (7).

Treatment options include surgical resection, chemotherapy, radiotherapy, or a combination of these. In addition, for a certain group of patients, expectant observation is preferred (7). These include patients with typical optic pathway/hypothalamic gliomas, especially in children with NF1, with non-progressive tumours in deep midline structures or the brain stem, where surgery would cause significant morbidity (7). Complete surgical resection, where feasible, is the treatment of choice as it may be curative, with the best chance of prolonged progression free survival (PFS) (8). However,

if only subtotal or incomplete resection is possible, the risk of progression or relapse is substantial.

Chemotherapy options include Vincristine and Carboplatin, or TPCV (Thioguanine, Procarbazine, Lomustine, Vincristine). Single agent Vinblastine has shown promising results for patients with progressive, unresectable LGG (9), as has Temozolamide (10). Other treatment options in refractory or progressive disease include Bevacizumab and Irinotecan (11).

Radiotherapy has a great role to play in patients with progressive or recurrent disease, or tumour that is inoperable at diagnosis (12,13). In appropriately selected patients, radiotherapy is more definitive than chemotherapy, with a 5 year EFS of 74.3% and OS of 98.5% (24). However, radiotherapy significantly increases long term morbidity, with an increased risk of second malignancies, significant neurological problems, such as seizures, blindness, coordination problems and endocrine problems such as growth failure, obesity and hypothyroidism (18).

Targeted therapy has developed rapidly over the last few years. The aim is to improve tumour control with the least side effects, resulting in better quality of life. An example includes mTOR inhibitors for Subependymal Giant Cell Astrocytomas (SEGA) associated with Tuberous Sclerosis (15). Although LGG in children represent a heterogeneous group of tumours, the majority of them involve the mitogen-activated protein kinase (MAPK) pathway. Mutations of the BRAF gene, which is part of the MAPK pathway, leads to cell cycle dysfunction. BRAFV600E mutations (point mutation leading to a valine to glutamate substitution at position 600) are found in varying degrees in the different subtypes of LGGs. For instance, they are found in 60-80% of pleomorphic xanthoastrocytomas, but only 5-10% of pilocytic astrocytomas. The presence of the

mutation is associated with poorer response to conventional chemotherapy and overall survival (16). Numerous clinical trials are investigating BRAF inhibitors, as they allow for targeted molecular therapy (17).

Long term overall survival amongst children with LGG is at least 83% in developed countries, even with incomplete tumour excision. There is a significant difference in overall survival however, between, Gr I and II LGG (14). Amongst long-term survivors of LGG, significant morbidity is experienced by many, including adverse neurocognitive effects, blindness, deafness, and serious endocrine sequelae (18). However, a study looking specifically at quality of life of children with LGG found that, despite tumour and/or treatment associated morbidity, children rated their quality of life higher than their peers (19). There is also a low likelihood of paediatric LGG related death in adult survivors, the greatest risk being associated with radiation exposure at a young age. It is thus important to minimize treatment-associated morbidity, especially related to radiotherapy (20).

There is little recent data available with regards to paediatric LGG in South Africa, as well as in developing countries as a whole. While some studies done in developing countries have shown similar epidemiological characteristics to published data in developed countries (21), others have shown poor outcomes for children with LGG (22). In addition, historically, little attention was paid to brain tumours at South African conferences (23).

Children with LGGs receive multidisciplinary care at Red Cross Children's Hospital and Groote Schuur Hospital, which forms part of the University of Cape Town's academic complex. Multidisciplinary care involves the departments of Neurosurgery, Radiation Oncology, Paediatric Oncology, Pathology, Radiology, with input from an educational

psychologist, occupational therapist and social worker. Integrated care for children with brain tumours has had a great impact on patients and their long term follow up (23).

Rationale

An audit of all children presenting with LGGs to Red Cross Children's Hospital and Groote Schuur Hospital since the active involvement of paediatric oncology in multidisciplinary management, especially looking at long-term outcomes for patients with LGGs. In addition, this study will be used to fulfil the requirements for an MPhil.

Objectives

1. This study will examine new data from 2013 - 2017, in addition to following up on the previous study done at this institution looking at data from 2001-2013 (HREC 389/2014). Data will be collected as was done previously (see data collection sheet). BRAF status was tested for in some patients since 2013, and this data, as well as time from initial symptoms to diagnosis, will be looked at in this study.

2. To analyse our management of children with LGG and determine outcomes, specifically looking at and comparing outcomes to other developing countries.

Methodology

4.1 Design

This study will be a retrospective data analysis.

4.2 Sample

Children treated for LGG at Red Cross Children's Hospital and Groote Schuur Hospital from 2001-2017.

4.3 Data

Data will be collected from patient folders at Red Cross Children's Hospital and Groote Schuur Hospital, and will be entered onto a Microsoft Access database.

4.4 Analysis

Statistica will be used to analyse treatment outcomes and will be represented on Kaplan-Meier curves.

4.5 Dissemination Plan

The data will be presented at SACCSG 2018 and SAPA 2018, as well as the University of Cape Town's Research Day in 2018.

Ethical Considerations

Patient confidentiality will be maintained, as patients' data are assigned numbers in the database, thus keeping patient's data anonymous. Informed consent is not indicated, as this is a retrospective study.

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Appendix 2: Data Sheet

Surname	Text	
Name	Text	
Folder number	Text	
Gender	Number	1=male 2=female
Birth date	Date/Time	
Age	Number	Years
Dxdate	Date/Time	
Histology	Text	
Dx Code	Number	1=WHO I 2=WHO II
Site	Text	
Site Code	Number	1=BS 2=Cerebellum 3=Optic Nerve 4= Hypothalamus 5=Thalamus 6=Cerebrum 7=Other
Metastases	Number	1=yes 2=no
Metastatic site	Text	
CSF +	Number	1=yes 2=no 3=not sampled
Dx2	Text	
NCSx	Number	1=NF 2=TS 3=nil
Headache	Number	1=yes 2=no
Cerebellar signs	Number	1=yes 2=no
Diplopia/eye signs	Number	1=yes 2=no
Endocrinopathy	Number	1=yes 2=no
Hydrocephalus	Number	1=yes 2=no
Seizures	Number	1=yes 2=no
Hypertension	Number	1=yes 2=no
Detail	Text	
Other	Text	
Prot	Text	
EVD	Number	1=yes 2=no
ETV	Number	1=yes 2=no
VPS	Number	1=at dx 2=at progression 3=never
VPS insertion	Number	1=RCCH 2=prior to referral
First line Rx	Number	1=surgery 2=RXT 3=Chemo 4=W&W
Second line Rx	Number	1=surgery 2=RXT 3=Chemo 4=W&W
Third line Rx	Number	1=surgery 2=RXT 3=Chemo 4=W&W
Surgery	Number	1=biopsy 2=debulking 3=total resection 4=nil
2nd Surgery	Number	1=biopsy 2=debulking 3=total resection
2nd Sx Date	Date/Time	
3rd Surgery	Number	1=biopsy 2=debulking 3=total resection
3rd Sx Date	Date/Time	
F/UDeth	Date/Time	
Stat	Number	1=ADF 2=SD on Rx 3=SD off Rx 4=PD 5=DD 6=DO 7=Lost 8=Lost PD
OS	Number	Months
OS censor	Number	0=uncensored 1=censored
HIVstatus	Text	1=positive 2=negative 3=unknown
Rec/Prog 1	Number	1=yes 2=no
R/P Dt	Date/Time	
Site Rec 1	Text	
PFS	Number	Months
PFS censor	Number	0=uncensored 1=censored
Rec/Prog 2	Number	1=yes 2=no
R/P 2 Dt	Date/Time	
Site Rec 2	Text	
Comment	Text	
Radiotherapy	Number	1=yes 2=no
Radiotherapy dose	Number	
Chemo 1	Text	
Chemo Response	Text	
Chemo 2	Text	
Chemo 2 Reason	Number	1=no response 2=progression off treatment 3=carboplatin sensitivity
Chemo 3	Text	

Chemo 3 Reason	Number	1=no response 2=progression off treatment 3=carboplatin sensitivity
Chemo 4	Text	
Chemo 4 Reason	Number	1=no response 2=progression off treatment 3=carboplatin sensitivity
HypoMagn	Number	1=yes 2=no
Endocrinopathy post Rx	Number	1=yes 2=no
Details	Text	
BRAF status	Number	1=positive 2=negative 3=unknown
Time from initial symptoms to dx	Date/Time	

Appendix 3: Ethics Approval

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

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

24 May 2018

HREC REF: 340/2018

Prof Alan Davidson
Radiation Oncology
Room 46, Ward G1
Red Cross War Memorial Children's Hospital

Dear Prof Davidson

PROJECT TITLE: LOW GRADE GLIOMAS TREATED AT THE UCT ACADEMIC HOSPITAL COMPLEX: 2001-2017 (MPHIL CANDIDATE - DR G KAHL)

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

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 May 2019.

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)

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.

The HREC acknowledge that the student, Dr Gisela Kahl will also be involved in this study.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical

Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI),and Declaration of Helsinki (2013) guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC 340/2018

Appendix 4: Ethics renewal

UNIVERSITY OF CAPE TOWN

HUMAN RESEARCH ETHICS COMMITTEE
14 OCT 2019
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	30.10.2020
☐ Not approved	See attached comments		
Signature Chairperson of the HREC	signature Removed	Date Signed	17/10/2019

Comments to PI from the HREC
Thank you for the deviation docunet

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	14/10/2019		
HREC REF Number	340/2018	Current Ethics Approval was granted until	30 May 2019
Protocol title	Low grade gliomas treated at the UCT Academic Hospital complex: 2001- 2017		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	☐ Yes ☒ No		
If yes, could you please provide the HREC Ref's for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Professor Alan Davidson		
Department / Office Internal Mail Address	alan.davidson@uct.ac.za		

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

Appendix 5: Author guidelines

Editorial Manager - Journal of Pediatric Hematology/Oncology

Journal of Pediatric Hematology/Oncology **Online Submission and Review System** **SCOPE** *Journal of Pediatric Hematology-Oncology* reports on major advances in the diagnosis and treatment of cancer and blood diseases in children. Each issue presents informative case studies and original research articles from leading clinicians and investigators worldwide.	Author Resources Instructions for Authors (this page) Reprint Ordering Permissions Requests Reprints

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Conflicts of interest
Authors must state all possible conflicts of interest in the manuscript, including financial, consultant, institutional and other relationships that might lead to bias or a conflict of interest. If there is no conflict of interest, this should also be explicitly stated as none declared. All sources of funding should be acknowledged in the manuscript. All relevant conflicts of interest and sources of funding should be included on the title page of the manuscript with the heading "Conflicts of Interest and Source of Funding:". For example:

Conflicts of Interest and Source of Funding: A has received honoraria from Company Z. B is currently receiving a grant (#12345) from Organization Y, and is on the speaker's bureau for Organization X – the CME organizers for Company A. For the remaining authors none were declared.

Compliance with NIH and Other Research Funding Agency Accessibility Requirements: A number of research funding agencies now require or request authors to submit the post-print (the article after peer review and acceptance but not the final published article) to a repository that is accessible online by all without charge. As a service to our authors, LWW will identify to the National Library of Medicine (NLM) articles that require deposit and will transmit the post-print of an article based on research funded in whole or in part by the National Institutes of Health, Wellcome Trust, Howard Hughes Medical Institute, or other funding agencies to PubMed Central. The revised Copyright Transfer Agreement provides the mechanism.

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The title page must also include disclosure of funding received for this work from any of the following organizations: National Institutes of Health (NIH); Wellcome Trust; Howard Hughes Medical Institute (HHMI); and other(s).

Unstructured Abstract and Key Words: Limit the abstract to 200 words. It must be factual and comprehensive. Limit the use of abbreviations and acronyms, and avoid general statements (eg, “the significance of the results is discussed”). List three to five key words or phrases.

Text: Organize the manuscript into four main headings: Introduction, Materials and Methods, Results, and Discussion. Define abbreviations at first mention in text and in each table and figure. If a brand name is cited, supply the manufacturer's name and address (city and state/country). All forms of support, including pharmaceutical industry support, must be acknowledged in the Acknowledgment section.

Abbreviations: For a list of standard abbreviations, consult the *Council of Biology Editors Style Guide* (available from the Council of Science Editors, 9650 Rockville Pike, Bethesda, MD 20814) or other standard sources. Write out the full term for each abbreviation at its first use unless it is a standard unit of measure.

CLINICAL AND LABORATORY OBSERVATIONS: Clinical observations may include case histories that demonstrate novel findings or associations, important clinical responses when a larger study is not needed to address a specific issue, or a unique laboratory observation linked to clinical care and/or practice. Text should contain 2500 words or fewer, with a brief abstract of 100 words or fewer. Abstracts outline background, observation(s), and conclusions. Include 4 illustrations and/or tables or fewer and 20 references or fewer.

MEDICAL PROGRESS: Review articles for this section should highlight what is particularly new and novel in a field related to pediatric hematology/oncology. Text should contain 5000 words or fewer and 100 references or fewer. Shorter reviews are encouraged and preferred. Authors considering submission should consult the Editor-in-Chief.

MORPHOLOGY CORNER: This section features photographs of especially interesting blood smears, bone marrow, or other tissue specimens that highlight an important aspect of hematology/oncology. Include an introduction of 200 words or fewer, the figure(s), a conclusion of 200 words or fewer, and 6 references or fewer.

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HISTORICAL INSIGHTS: Historical insights include concise descriptions or analyses of historical importance in the field of pediatric hematology/oncology. These may include personal descriptions of historical figures, important papers, and interesting occurrences that led to advancements in pediatric hematology/oncology. Photographs and artwork are welcome. Text should contain 2500 words or fewer and include 25 references or fewer. All material should be original **or carry permission for publication.**

LETTERS TO THE EDITOR: Letters to the editor should pertain to articles published within the *Journal of Pediatric Hematology/Oncology* or highlight important new clinical or laboratory insights. Text should contain 500 words or fewer.

BOOK REVIEWS: Reviews of books should relate to topics relevant to pediatric hematology/oncology, including immunology and transplantation. Text should contain 1000 words or fewer.

ANNOUNCEMENTS: Announcements should be submitted 6 months in advance of the event date and may include scheduled meetings, symposia, postgraduate courses, and other announcements of interest to specialists in pediatric hematology/oncology.

References: The authors are responsible for the accuracy of the references. Key the references (double-spaced) at the end of the manuscript. Cite the references in text in the order of appearance. Cite unpublished data—such as papers submitted but not yet accepted for publication and personal communications, including e-mail communications—in parentheses in the text. If there are more than three authors, name only the first three authors and then use et al. Refer to the *List of Journals Indexed in Index Medicus* for abbreviations of journal names, or access the list at http://www.nlm.nih.gov/tsd/serials/lji.html. Sample references are given below:

Journal Article
1. Ang KK, Price RE, Stephens LC, et al. The tolerance of primate spinal cord to re-irradiation. *Int J Radiat Oncol Biol Phys*. 1993;25:459–464.

Book Chapter
2. Dimery IW. Chemotherapy in head and neck cancer. In: Myerhoff WI, Rice DH, eds. Otolaryngology: head and neck surgery, 2nd ed. Philadelphia: WB Saunders, 1992:1027–1045.

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Database
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World Wide Web
7. Gostin LO. Drug use and HIV/AIDS [*JAMA* HIV/AIDS Web site]. June 1, 1996. Available at: http://www.ama-assn.org/special/hiv/ethics. Accessed June 26, 1997.

URL (Uniform Resource Locator)
8. (J. M. Kramer, K. Kramer [jmkramer@umich.edu], e-mail, March 6, 1996).

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Here are the basics to have in place before submitting your digital artwork:

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Remember:

- Cite figures consecutively in your manuscript.
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