The Changing Face of Craniopharyngioma Treatment in Young Children and its Challenges at a Single Centre in a Developing World Context

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Declaration

I Ncedile Mankahla hereby declare that the work on this dissertation is based on my original work (except where acknowledgements indicate otherwise) 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.

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Abstract

The Changing Face of Craniopharyngioma Treatment in Young Children and its Challenges at a single Centre in a developing World Context.

Objective: To retrospectively review our institutional experience with the treatment of paediatric craniopharygiomas and assess the evolution in management and influence on patient outcomes.

Patients and Methods: A retrospective review from January 1995 to December 2015 of children age <14 treated at a single institution. Data collected included admission clinical features, endocrine function, surgery performed, surgical outcome, intracystic therapy and radiotherapy. Long-term functional outcome was calculated considering hormonal dependence, level of independence and schooling.

Results: There were 41 patients with a mean age of 84.2 months: 57% were female. Primary surgical resection was performed in 36 patients: 80.5% had subtotal resection, 11% had gross total resection and the rest had biopsy only. Of surgical approaches, 60,7% had pterional craniotomy and 39,2% supraorbital keyhole craniotomy. No surgical mortalities occurred but 2 patients had new post-operative neurological deficits. Stereotactic placement of intracystic catheters transitioned to endoscopic. Intracystic treatments transitioned from Yttrium (1) to Bleomycin (6) to Interferon Alpha (6). Radiotherapy was given in 30 patients, median dose 54Gy. Final Wen functional outcome was 21,8% Class I, 32% Class II and 46% Class III. There were no early deaths in the series but 5 patients died more than 6 years after diagnosis, mostly due to endocrine crises from poor chronic care.

Conclusion: The findings reflect a multidisciplinary team approach consisting of maximal safe resection with radiotherapy, intracystic agents and endocrine support. For a cohort limited to young children, our results are similar in number and outcomes to other published series. Mortality remains low but lifelong dependence on endocrine replacement is a significant contributor to long-term morbidity and mortality. This has important implications for patients referred from large distances and where primary and secondary follow up care is poor.

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Abbreviations

ACTH – Adenocorticotrophic Hormone
ADH – antidiuretic hormone
APC – adenomatous polyposis coli
CSF – cerebrospinal fluid
CT- computerized tomography
CTSP – cape town stereotactic pointer
DDAVP - desmopressin
DI – diabetes insipidus
ETSS – endoscopic transsphenoidal surgery
FSRT – fractionated stereotactic radiotherapy
GH – Growth Hormone
GTR – gross total resection
IMRT – intensity modulated radiotherapy
IFα - interferon alpha
LINAC – linear accelerator
MDT – multidisciplinary team
MRI – magnetic resonance imaging
PRL – Prolactin
RT – radiation therapy
SD – standard deviation
STR – subtotal resection
TSH – Thyroid Stimulating Hormone
QoL – quality of life
VEGF – vascular endothelial growth factor
WHO – world health organisation

Section A

Background/ The Setting

Craniopharyngiomas are benign brain tumours arising from the middle skull base, related to the pituitary gland and infundibulum. Epidemiology and demographic patterns are poorly described because the disease is rare. Furthermore, brain tumour registries largely collect data for malignant tumours and leave many lesions under reported. Our understanding of these tumours is derived from first world literature, from non-African population groups who are exposed to different resources.

In South Africa, due to the enormous burden of communicable diseases and trauma within an emerging economy, primary health care is the focus of resource investment. Brain tumours fall under tertiary health care. Such tertiary centres are the most resource intensive, requiring specialists and specialized equipment, leading to centralization. No more than two or three are accommodated in a province. This structuring presents challenges to the management of brain tumour patients. People have to travel large distances to access needed health care, access to follow up is difficult. Management prescriptions and approaches that require close patient monitoring become difficult. For example, a patient treated with surgical resection only and no radiation therapy will require repeat hospital visits to monitor for recurrence. Given the difficulties with follow up and access, should this risk be taken, given the possibility of loss to follow up and late presentation with unsalvageable recurrence? Or should all receive preventative radiation therapy with all its attendant risks to protect against such loss to follow up? These questions may be less important in high-income countries but must be considered when resources are constrained. These factors have implications for treatment and so a local analysis of practices and outcome is needed.

Craniopharyngioma is a useful example of a tertiary care driven condition to examine for several reasons. First, dedicated specialised services in skills and equipment are needed. Experienced paediatric neurosurgeons are ideal if

possible. In addition to expertise, they require tools - microsurgical and endoscopic and occasionally navigation. Similarly, radiotherapy services are essential and must be accessible. Endocrine support is also critical. Following on this, a multidisciplinary approach to decision-making is essential. Ideally, there should be a multidisciplinary clinic that jointly manages children and decides on priorities. Finally, this is a chronic condition that often presents in childhood but has to be actively managed over many years of life expectancy. Understandably, there are several challenges to meeting these requirements in a developing world setting.

For the above reasons, we aimed to examine the treatment and outcomes of young children with craniopharyngioma in a single centre in South Africa to characterise the patient population, describe their treatment outcomes and identify factors that may be challenges in the developing world context.

We aimed to examine young children (age 13 or less) who presented for treatment. In part this represents the patient population that presents to the Red Cross Children's Hospital, and in part it reflects the patient population managed through the multidisciplinary clinic. The age range is particularly important when comparing to published series, most of which include children up to age 16 or 21, and/or adults.

Overview of the thesis and Layout

Chapter 1: A review of current knowledge about craniopharyngiomas is discussed presenting understanding of relevant anatomy and embryological origins. It discusses how treatments have changed over the years. A summary analysis of reported outcomes on overall mortality and specifically perioperative mortality has been performed and presented. Important issues around clinical presentation, hormonal deficiencies and attempts to characterise tumour related features that influence treatment and outcome. We review the history and evolution of oncological management including intracystic therapy, radiation oncology techniques and how these have influenced the approach to surgical resection.

Chapter 2

This chapter presents our results and is divided into sections that cover important stages in the management of craniopharyngioma patients, along with observations that may have an influence on outcome. Surgical results and their influence on morbidity are reported independently, followed by endocrine and oncological findings. An attempt is then made to classify survivors according to the level of function to determine an overall picture of the influence of treatment on outcome.

Methodology Overview

This was a retrospective folder review. Sources of data included databases from neurosurgery, radiation oncology, endocrinology and radiology. Further details are included in chapter 2.

Due to the rarity of these tumours, meaningful information could be obtained only from long-term experience. The time span was 20years up to and including 31 December 2015. Although literature defines paediatric as age <19, our definition was age <14, reflecting the admission age limit at Red Cross Children's Hospital. Because craniopharyngioma is a benign lesion with long term survival but compromised quality of life, data capture focused on indexes that would reflect that quality of life, endocrine status, surgery type and radiation oncology.

Chapter 1

Introduction and Literature Review

Craniopharyngiomas are rare epithelial tumours of the parasellar region, thought to arise from remnants of Rathke's pouch along the path of the craniopharyngeal duct. Although benign with high survival rates, the quality of life (QOL) in these patients is frequently poorer than the general population. This is a function of both tumour location and treatment sequelae. Craniopharyngiomas have two distinct histological subtypes: the adamantinomatous type, common in children, frequently cystic with calcifications and the papillary subtype, occurring exclusively in the adult population. Evidence suggests that these tumours are biologically and embryologically distinct.

History:

The first description of a craniopharyngioma was in 1857 by the pathologist Friedrich von Zenker, from an autopsy case. Already by this time Martin Rathke had described embryological origin of the pituitary gland from the anterior foregut (1). The term craniopharyngioma was coined by Charles Frazier and popularized by Harvey Cushing, but Halstead was the first to successfully resect these tumours. Over the course of the 20th century, operative management of these lesions evolved from aggressive surgery with dismal outcomes to slight improvement with the introduction of corticosteroids, penicillin and the operating microscope(2). Matson and Ingraham were among the first to describe outcomes with perioperative corticosteroid administration(3). Further improvements in patient outcomes were aided by introduction of computerized tomography (CT) In 1974, the resurgence of endoscopic surgery to the modern microsurgical era, peaking in the 90's. Modern strategies such as radiation therapy and intratumoral chemotherapy have transformed craniopharyngioma care from a mortality prevention strategy to quality of life preservation objective.

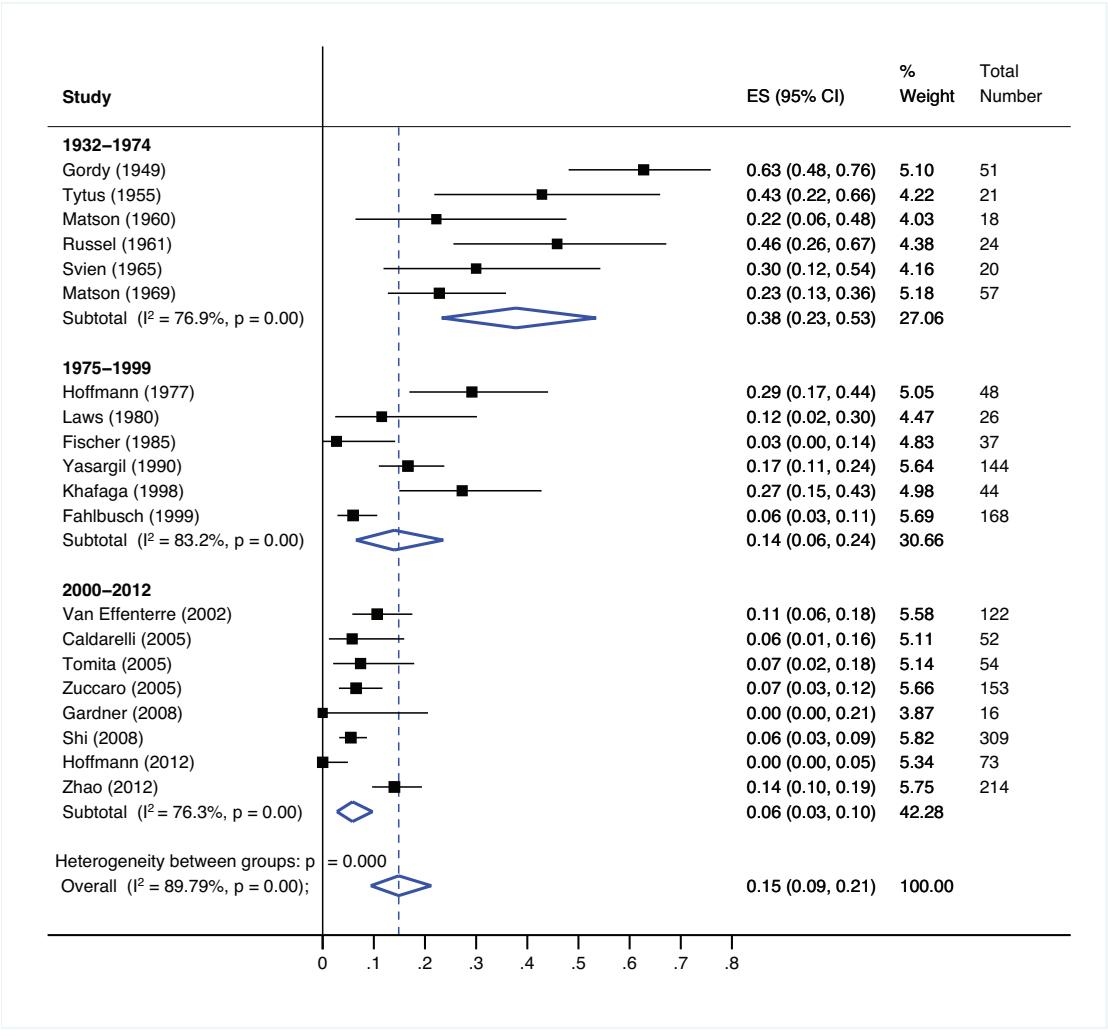

Table 1: summary of overall mortality over eight decades in surgical series. A trend of decreasing mortality is seen reflecting improved therapies.

A progressive decrease in perioperative mortality has been seen over the past seven decades as neurosurgical techniques have improved in sophistication. Microsurgery was introduced into neurosurgery in 1967(4). After this, advocates of radical tumour extirpation grew. Endoscopic surgery brought increased safety and improved morbidity. Table 2 summarizes these outcomes through an analysis of published surgical reports. Only those that reported perioperative mortality, defined as death within thirty days of surgery were included. Many studies combined paediatric and adult data, this could not be separated on analysis. Mortality at primary and reoperations in each study were grouped into a single final outcome.

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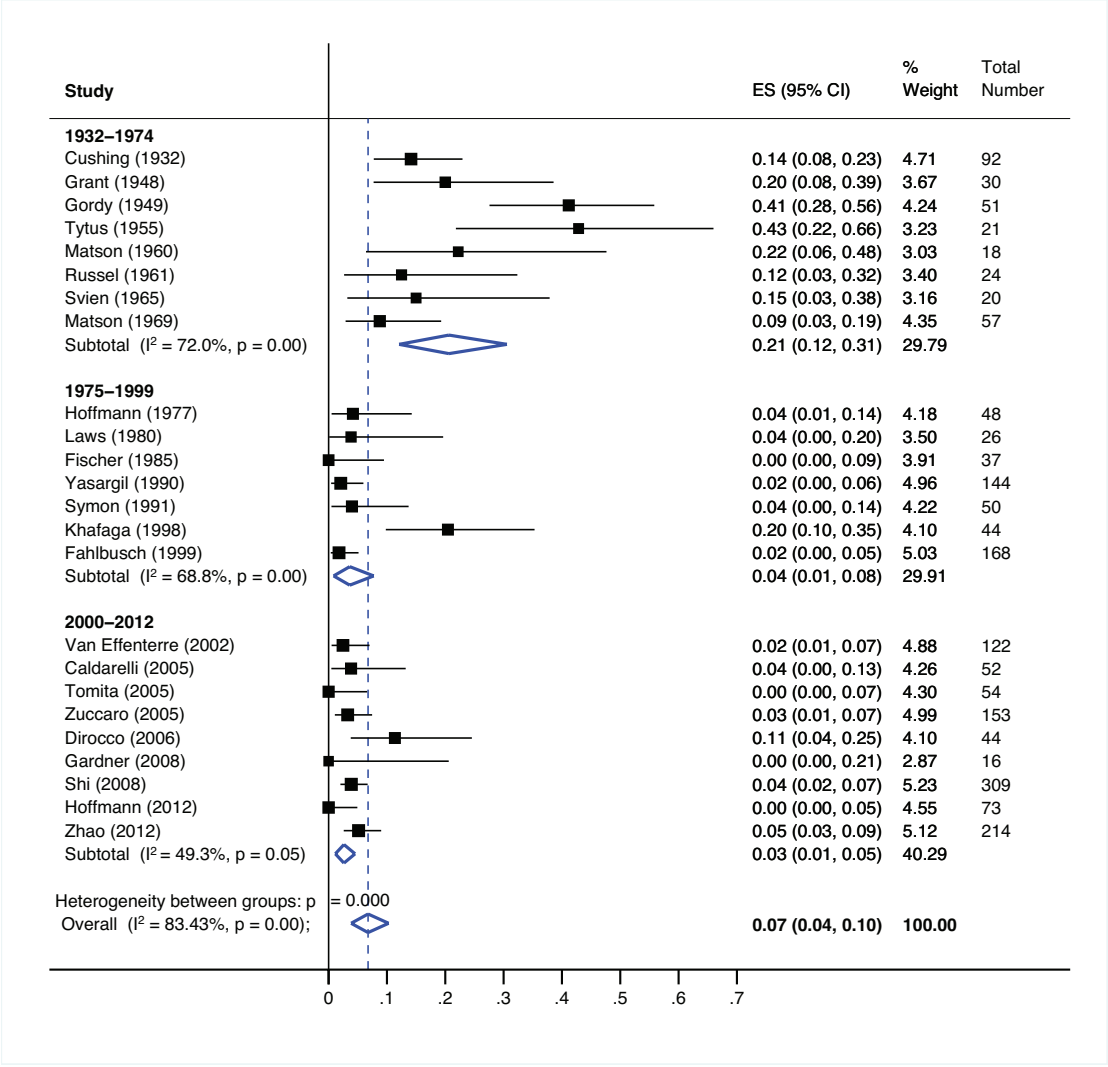


Table 2: Forest plot demonstrating perioperative mortality in the decades following Cushing's report on his experience in 1932

Epidemiology:

Craniopharyngiomas account for 3% of brain tumours overall but 10% of paediatric brain tumours and are the most common suprasellar tumour in the paediatric population(5). No data exists from South Africa and statistics from the National Cancer Registry do not specify brain tumour subtype. Internationally, the incidence is 0,13 per 100,000 per year and does not vary by gender(6). There is a bimodal age distribution with a peak in children (5-14years) and adults (65-74years). Survival is higher among children although comparison is difficult due to difference in tumour subtype.

Embryology:

Craniopharyngiomas arise from the pituitary stalk, thus the embryological origin follows the development of the pituitary gland and stalk. The pituitary gland develops from two distinct parts of the embryo. The posterior pituitary or neurohypophysis originates as a downward growth of neural tissue from the floor of the diencephalon, as the infundibulum. This begins in week 4. Simultaneously, the roof of the primitive oral cavity or stomodeum develops a dorsal diverticulum, anterior to the buccopharyngeal membrane. This dorsal evagination of the stomodeum is termed Rathke's pouch. This pouch ascends through chondrification centers of the developing sphenoid bone and connects with the anterior and lateral surfaces of the descending infundibulum(7). The path taken by the Rathke's pouch is termed the craniopharyngeal duct.

Two theories have been postulated to explain the pathogenesis of craniopharyngiomas, namely the Embryogenic theory and Metaplastic theory.

- Embryogenic theory: this hypothesis suggests that embryogenic squamous cell nests along the path of the involuted craniopharyngeal duct undergo neoplastic transformation. This theory is supported by the typical microscopic composition of calcifying squamous epithelium that resembles odontogenic tumours.
- Metaplastic theory: Residual squamous epithelium in the adenohypophysis and anterior infundibulum undergoes neoplastic transformation. This theory suggests that tumours arise from metaplasia of mature components of the anterior pituitary, rather than embryonic remnants(8).

It is likely that these theories simply describe the two varieties of craniopharyngioma. The adamantinomatous variety, largely cystic, with calcification most closely resembling odontogenic tumours probably fits into the embryogenic theory. The exclusively adult papillary tumour, infrequently calcifying or cystic is likely accounted for by the metaplastic theory. This adds to the idea that, although these lesions share a common name, they should be treated as distinct clinical and biological entities.

Pathology and Molecular Oncogenesis:

Craniopharyngiomas are histologically benign World Health Organisation (WHO) Grade I lesions(9). The adamantinomatous tumours occur at both age peaks but most frequent in children. Macroscopically, they vary from predominantly solid, to entirely cystic in 15% of cases or more commonly in 70% of cases partially cystic and solid(10). The cystic fluid varies in appearance from dark “machine-oil” like, to shimmering yellow. This fluid contains desquamated epithelial cells and cholesterol crystals. The majority of these lesions (80%) have calcifications. Microscopically, the tumours resemble adamantinoma of the jaw and calcifying odontogenic cyst(11). They have trabeculae of squamous epithelium with clusters of wet keratin. Papillary variants occurring exclusively in adults are frequently solid with just over 50% having cystic components and 45% have calcifications. Microscopically they have solid sheets of squamous epithelium with fibrovascular stroma. They may have foci of cilliation and goblet cells, wet keratin is characteristically absent(12)(13).

Genetic and molecular characterization of these tumours has been hampered by their rarity. It is recognized however that chromosomal deletions, amplifications and translocations play an important role in tumour genesis. Papillary craniopharyngiomas have demonstrated no recurrent mutations to implicate in their genesis. Vascular Endothelial Growth Factor (VEGF) expression increase is present but not unique to these tumours. P53 tumour suppressor gene mutations are absent(14). More promising results have come from the demonstration that adamantinomatous craniopharyngiomas have intracellular accumulation of β-catenin(15). Beta-catenin is a dual function protein and a downstream component of the Wnt signal transduction pathway. This is involved in regulation of cellular proliferation, morphology and development. Genes encoding β-catenin, Catenin Beta 1 (CTNNB1) and Adenomatous Poliposis Coli (APC) are characteristic only in the adamantinomatous variant(16)(17)(18)(12)(19).

Natural History and Clinical Difficulties:

Although histologically benign, these tumours can have an aggressive clinical course. Craniopharyngiomas are lifelong afflictions with a tendency to recur. The rate of recurrence increases with duration of follow up. The principal difficulty is a result of location. The most frequent site of occurrence is the suprasellar space. Here the tumour is in close proximity to neural and vascular structures that are sensitive to treatment effects. Adherence to the pituitary stalk and hypothalamus is frequent, increasing the risk of organ dysfunction from pressure effects of the tumour and injury with treatment modality. The pituitary gland, optic chiasm are also commonly distorted. Vascular structures surrounding the lesions include the basal circle of Willis and the cavernous sinuses. Consequently, vision, endocrine and neurobehavioural function are at risk in the patient.

Clinical Manifestation

Presentation of craniopharyngioma is determined by the location, size and direction of growth. Symptoms vary from non-specific signs of raised intracranial pressure, visual impairment to overt coma from hydrocephalus. Behavioural and cognitive dysfunction, including decline in scholastic performance may also be presenting features. Only a minority of patients seek medical help from an endocrine related complaint, even though these are frequent abnormal findings(20). The most common presenting complaint is non-specific headache and nausea. Symptoms of raised intracranial pressure occur more frequently in children than in adults. In a retrospective series of 121 paediatric and adult craniopharyngiomas, Karavitaki et al reported headache as the dominant presenting complaint in 64% of patients. Van Effenterre and colleagues, in their series reported headache as the second most common presenting complaint at 53%, after visual deficits which were present in 75% of patients(21,22). In this same series, decreased visual acuity was documented in 80% of patients, while field deficits were present in 79%. The median time delay from symptom onset to diagnosis is reported at 12-27months(8).

Endocrine dysfunction at presentation is present in up to 90% of patients. Growth hormone (GH) deficiency is the most frequent, occurring in 80-100% of patients. Hypogonadism occurs in 75-80%, adrenocorticotrophic hormone (ACTH) deficiency 30-60% and hypothyroidism is found in 20-40% of patients. The most infrequent is diabetes insipidus, being found in only 7-20% of patients(23,24). Pathological reduction in growth velocity is also seen in approximately 33% of craniopharyngioma patients, while weight gain frequently manifests after treatment(25). Cognitive decline in adults and deteriorating school performance in children is not an infrequent complaint at presentation. Ocular motor neuropathy and limb weakness in the absence of hydrocephalus are uncommon.

Diagnosis and Imaging

The combination of headache, poor vision, decreased growth rate and cystic suprasellar mass can be clinically diagnostic of craniopharyngioma.
Imaging evaluation is with computed tomography (CT) and magnetic resonance imaging (MRI), which are complementary. X-ray, which can show calcifications in and around the sella is not routinely utilized.
CT – this is frequently the screening modality in symptomatic patients. This also is the principal diagnostic and follow up modality for hydrocephalus. It should be performed with and without contrast administration. The bone window will reveal calcifications which are present in 90% of paediatric craniophanygniomas, this number drops to 45-50% in adults. The sella turcica is frequently not expanded, unlike in pituitary macroadenomas. There may be erosion of the dorsum sellae or expansion with calcific rim. Cysts are isodense to cerebrospinal fluid (CSF) on CT and the solid component enhances in the majority(26).

MRI is the most important imaging modality. It is valuable in diagnosis, planning of appropriate therapeutic strategy, early post-operative evaluation of extent of resection and in assessment for recurrence. Multiplanar T1 weighted images with gadolinium are essential. These delineate the enhancing solid component, frequently in the sella with a suprasellar cyst(27).
Craniopharyngiomas are commonly T1 hyperintense, the cyst may have

heterogenous intensity related to protein and cholesterol content. T1 fat suppressed image will reveal the posterior pituitary bright spot. In small tumours, the gland can be differentiated from the tumour. It is often compressed within the sella(28).

Various imaging-based criteria have been proposed to classify location and growth of craniopharyngiomas with the view of predicting clinical outcome and extent of surgical resection. The relationship of the tumour to the wall of the third ventricle is most important surgically. This determines the resectability of a tumour and expected morbidity. Many attempts have been made to classify these growth patterns. Table 3 and 4 summarize descriptions of growth patterns and predictors of hypothalamic involvement(29). Determination of tumour size is important because it is correlated to recurrence rate and extent of resection. Tumours greater than 5cm have an 80% recurrence rate while those less than 5cm a 20% recurrence rate(28). Sainte-Rose et al, in their study of surgical management of craniopharyngiomas determined that surgical treatment should be guided by preoperative hypothalamic involvement(30). Yasargil and later Zuccaro, further classified tumours according to size. Small were tumours <2cm, moderate 2-4cm, large 4-6cm and giant those greater than 6cm(4,31).

Table 3: summary of classification systems for hypothalamic involvement(30,32,33)

Grade	Description
De Vile (1996)	
0	No visible damage
1	V3 floor thickened
2	V3 floor thinned or distorted
3	Small breach in tuber cinereum
4	More extensive breach than grade 3
5	Floor of third ventricle completely deficient
Sainte-Rose (2005)	
Type 0	No involvement of hypothalamus
Type 1	Hypothalamus elevated / distorted but visible
Type 2	Hypothalamus involved and no longer visible
Puget (2007)	
Grade 0	No hypothalamic involvement
Grade 1	Tumour abuting or displacing hypothalamus
Grade 2	Hypothalamus no longer identifiable

Table 4: classification systems of tumour growth patterns(4,34,35)

Hoffman (1977)	
Type A	Sellar
Type B	Chiasmatic
Type C	Third ventricle floor (pre and retrochiasmatic)
Type D	Intraventricular
Samii (1997)	
Grade I	Intrasellar / infradiaphragmatic
Grade II	Occupying suprasellar cistern
Grade III	Lower half of third ventricle
Grade IV	Upper half of third ventricle
Grade V	Reaching septum pellucidum or lateral ventricles
Yasargil (1990)	
Type a	Purely intrasellar /infradiaphragmatic
Type b	Intra and suprasellar
Type c	Supradiaphragmatic, paraventricular
Type d	Intra/extraventricular
Type e	Paraventricular in respect to v3
Type f	Purely intraventricular

Principles of Management

The decision-making process in primary treatment of craniopharyngiomas is influenced by many factors. Patient, tumour and treatment related considerations determine the optimal strategy. Sometimes, prior to addressing the tumour, hydrocephalus may be an emergency requiring attention. Surgery is nearly always performed, but multimodality interdisciplinary management is still the cornerstone of care and must be individualized(36). Options vary from limited to radical surgery, influenced by characteristics of the tumour (size, consistency, location), the age and clinical state of the patient, as well as surgeon experience and training. In cystic tumours, intra-cystic chemotherapy is an attractive option, particularly in the very young, with limited morbidity associated with insertion and modern agents.

Radiation therapy has emerged as a safe and indispensable tool for long-term control. Conventional fractionated external beam radiotherapy, precision stereotactic fractionated radiotherapy and radiosurgery have improved accuracy and safety. Heavy particle therapy with protons has been studied to improve radiobiological profile and outcomes(37–41).

Surgery

The goals of surgery include biopsy, resection (total and subtotal) and insertion of catheters for intra-tumour therapy. Insertion of catheters to decompress neural structures and instil intra-cystic chemotherapy can be done open via a craniotomy, stereotactically with a bur hole and through endoscopic assisted surgery. Resective surgery has evolved from proponents of aggressive resection, to a more contemporary approach of limited surgery with adjuvant radiation therapy(4,31,42,43). This move has been influenced by long term outcome data that supports sustained tumour control and preserved QoL with radiation therapy(44–46). Surgical approaches may be endoscopic, utilising the trans-sphenoidal route, or transcranial, namely pterional and supraorbital key-hole craniotomies that utilize the subfrontal corridor. The former also allows a trans-sylvian corridor. Considerations in

surgical approach include size, extent and location of the tumour relative to the optic chiasm. Pre-chiasmatic tumours are easily accessible through the subfrontal corridor while retrochiasmatic tumours are reached with some difficulty thought this route. Retro-chiasmatic tumours are also more likely to invade the hypothalamus. The extent of resection is classified into biopsy, subtotal and gross total resection (GTR). Size >4cm and retrochiasmatic extension has been associated with limited GTR(47). Distinction also exists between planned subtotal and that occurring with initial intent to GTR.

Radiation Therapy

There has been a growing shift towards limited surgery and planned adjuvant radiation therapy for craniopharyngiomas. Evidence has shown comparable tumour control rates with limited surgery and radiation therapy, along with a favourable QoL outcome(48). A report by Merchant et al on the St Jude Hospital experience showed that children who received radical surgery lost 9.8 full scale IQ points *vs* 1.25 points in a limited surgery and radiotherapy group ($p<0.063$)(49). A recent systematic review on predictive factors for recurrence in craniopharyngioma noted the presence of residual tumour and skipping radiation therapy to be risk factors(50). In the multicentre, prospective surveillance Kraniopharyngeom 2000 study, risk of progression at 3years was 80% lower In irradiated children(51). All modalities have been studied including fractionated conventional and stereotactic radiotherapy, intensity modulated radiotherapy used to shape beams and conform to the lesion, as well as radiosurgery(52–55).

Intracystic Therapies

Local radiotherapy or brachytherapy with β-emitting isotopes is now of historical interest. Substances used were Yttrium-90, phosphorus-32, rhenium-186. Characteristics of these agents were low tissue penetration with favourable half-life. Phosphorus-32 has a half-life of 14.3days with tissue penetration of 2-8mm, Yttrium-90 has 2.7day half–life and 11mm tissue penetration(56). Recurrence and survival rates were however inferior to surgery and radiation therapy(57).

Bleomycin: this is an antitumoral glycopeptide antibiotic used to treat squamous cell carcinoma. Due to the epithelial component of childhood craniopharyngioma, efficacy in these tumours was suggested as likely. Therapeutic benefit with this agent is derived from the control of cyst growth but not solid tumour. It does not penetrate the blood brain barrier thus cannot be administered systemically. Its effects are on the G, M and S phases of the cell cycle(58). Though used widely and effectively in tumour cyst control, toxicity and hypothalamic injury from leakage have influenced a move to other agents(59)(60).
Interferon Alpha: Ifα is also a tumour sclerosing agent used in squamous cell carcinoma. It is currently the agent of choice for intra-cystic therapy. It has excellent cyst growth control and reported to be well tolerated if there is ventricular leakage(61–63).

Functional Outcomes after Treatment

With sophistication of treatment modalities, long-term survival occurs in the majority of patients. Survival rates at 3 years, 5 years and 10 years are 97%, 96% and 93% respectively(51). The quality of that survival has become the principal objective.
Endocrine effects: As stated, admission endocrine deficits are present in up to 85% of patients, growth Hormone deficiency being the most common. Restoration of previously deficient hormones is exceptionally rare. The extent of surgery has the strongest influence on new endocrine dysfunction. Transient post-operative diabetes insipidus (DI) occurs in nearly 100% of patients. Permanent (DI) occurs in 80-93% of patients who undergo GTR, GH deficiency occurs in 75%(64). Replacement in pre-pubertal children is recommended and safe. Because radiotherapy is often adjuvant, pre-irradiation endocrine deficits are common(65). Loss of previously present hormonal function after radiation is known and begins after 12months of treatment, growth hormone is the most frequently occurring. Onset is dose dependent while severity is influenced by dose per fraction.
New neurological deficits: Vision deterioration after surgery is infrequent and influenced by preoperative deficit and a pre-chiasmatic tumour location. New

motor deficits are rare and when present are transient. Late effects of radiation therapy including carotid vessel occlusion are very uncommon. Hypothalamic and cognitive dysfunction: This is one of the most debilitating consequences among survivors. The hypothalamus has multiple functions in the body including control of circadian rhythm, regulation of the autonomic nervous system including sympathetic control of lipolysis. Symptoms of dysfunction include obesity, fatigue, behavioural changes, blood pressure, temperature and heart rate dysregulation. Rapid weight gain is the most frequent complication of hypothalamic dysfunction. In a review of childhood obesity after craniopharyngioma treatment, Rosenfield found a trend towards obesity over time, at diagnosis 17% were obese vs 46% at follow up(66). Qi et al found a close association between tumour location near the floor of the third ventricle and development of new obesity(67). Cognitive dysfunction is also more common in paediatric patients with craniopharyngiomas. Disturbances in memory, attention, impulse control and socialization are present.

In an attempt to create a standardized metric or rating scale for pre and post-operative function, a number of functional scales exist. Many are comprehensive but difficult to apply practically. De Vile described a comprehensive scale with multiple variables including endocrine dysfunction, vision status, neurological dysfunction and education, this was modified by Elliot et al(32,68). A more readily applicable scale however is one described by Wen et al, a scale that stratifies patient function into grades I-IV(69). Grade one being grossly normal and independent, IV being entirely dependent on self-care. Grade II includes independent patients with endocrine dysfunction and moderate visual impairment, while grade III denotes severe visual impairment with focal neurological dysfunction.

In stratifying patients according to functional outcome scales, it is hoped that associations in time can be made between level of function and intervention received to help modify treatment accordingly.

Chapter 2

Methods

Study Design

This was a retrospective folder review of patients admitted at Red Cross Children's and Groote Schuur Hospitals. Sources of data included databases from neurosurgery, radiation oncology, endocrinology and radiology. Where data were missing from these sources, folders were extracted for chart review.

Patient selection

Patients were selected according to an existing paediatric neurosurgery and oncology database according to diagnosis. Only patients below the age of fourteen years at diagnosis were included, in accordance to the admission age limit at the Children's Hospital. Although adolescents fall under a general acceptance of paediatric care in most centres, the treatment of these at our institution falls under adult neurosurgery, so were not included. Patients who received primary treatment at other institutions and subsequently referred to us were included only if prior treatment information was available. Those with missing pretreatment data were excluded from analysis. Inclusion dates were from January 1995 to 31 December 2015, thus constituting a 20year review.

Data collection

The following data categories were collected:

Demographics: age, sex

Presenting Clinical Features: symptoms and sings, and admission endocrine findings.

Imaging and Intervention:

Pre-operative imaging: size was defined into ordinal categories (small, intermediate, large and giant), relationship of tumour to the hypothalamus and appearance (solid, cystic or mixed). Only MRI with sagittal images was used to assess the relationship of tumour to the hypothalamus.

Post-operative imaging: quantifying extent of resection (CT/MRI) into Gross Total Resection (GTR), Subtotal Resection (STR) or Biopsy.

Type of surgery: placement of reservoir and method, craniotomy for resection and operative detail and operative complications (neurological and endocrinological).
Surgical mortality was defined as death within 30 days of surgery.

Long term follow up information was collected form the multidisciplinary clinic records in the radiation oncology department at Groote Schuur Hospital.

Privacy and Confidentiality:
All data were deidentified for analysis.

Statistical Analysis
This is primarily a descriptive study. Descriptive statistics were used to characterize the total sample and compare presenting symptoms and endocrine function. Continuous variables are described using means (standard deviations) and medians (interquartile ranges) depending on their distribution. Categorical variables are presented as frequencies and percentages.

Chapter 3

Results

Patient population

A total of 41 patients were identified, with mean age at presentation of 84.2 months, 57% were female. The age ranged from 1year to 13 years. This was a limited age range owing to the exclusion of adolescents up to 18years who are treated at the adult hospital. The median follow up period was 83.5 months. All patients had clinical examination to detect visual deficit but only 31 patients had documented formal preoperative vision assessment by an ophthalmologist. Table 5 summarizes the presenting clinical features.

Table 5: presenting features and examination findings as documented in clinical notes.

Admission clinical features	n (%)
Visual deterioration	23 (56)
Headache	23 (56)
Acute hydrocephalus	18(43.9)
Short stature	11(26)
Disturbed consciousness	6(14)
Learning difficulty	5(12.1)
Motor weakness	5(12.1)
Cranial nerve abnormality	4(9)
Seizures	3(7.3)
Behavioural problem	2 (4.8)
Obesity	2 (4.8)

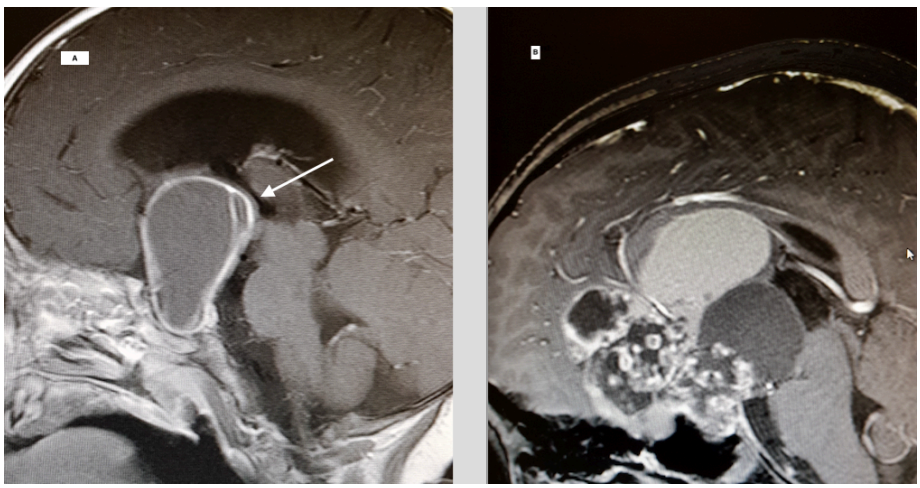
Imaging

Preoperative imaging prior to 2000 consisted of CT only. Imaging characteristics were obtained either from available images or printed radiologist reports with tumour dimensions. Thirty-four patients had adequate data for volume assessment. Figure 1 shows typical examples of hypothalamic invasion grading. There were 2 cases of intra-sella tumours, the remainder extended to the suprasellar space. Hydrocephalus occurred in 43.9%. These findings are summarized in table 6.

Table 6: Summary of MRI tumour characteristics. Hypothalamic involvement evaluated according to Sainte-Rose grading system(30).

Tumour size (34 patients)	n (%)
Small (<2cm)	2 (5.8)
Medium (2-4cm)	16 (47)
Large (2.1-6cm)	5 (14.7)
Giant (>6cm)	11 (32.3)
Tumour consistency (40)	
Cystic >50%	26 (65)
Solid	3 (7.5)
Mixed	11 (27.5)
Hypothalamic involvement (31 MRIs)	
Type 0	4 (12.9)
Type I	13 (41.9)
Type II	14 (45.1)

Figure 1: gadolinium contrast enhanced mid-sagittal MRI scans of two different patients demonstrating two types of hypothalamic involvement a) moderate size cystic craniopharyngioma Sainte-Rose Type I, hypothalamus is displaced but visible (arrow), b) giant multicompartment tumour Type II, the hypothalamus is no longer visible.



Surgical results

All but 4 patients had attempted surgical resection. Of the four who were not operated on, 2 had small intra-sella tumour and were observed, 2 had Ommaya catheter insertion only with no resection attempt. These outcomes were dichotomized according to approach and extent of resection. Gross total resection (GTR) was defined as absence of visible enhancing tumour or capsule on post operative MRI or CT. The choice of surgical approach was also evaluated between traditional craniotomy (large hemi-coronal flap and subfrontal approach) and supraorbital keyhole craniotomy.

A total of 36 patients had surgical resection, one patient's surgical results were omitted as he was operated on at another institution and referred to us for adjuvant therapy. There were 3 who had biopsy alone, 29(80.5%) had subtotal resection, 4(11%) had gross total resection. Surgical approach could be determined in 28 cases, of which 17(60.7%) had traditional craniotomy vs 11(39.2%) with the supraorbital keyhole approach. Of the four GTRs, two were through pterional approach and two through supraorbital keyhole. All of the supraorbital keyhole craniotomies were performed after 2002. Only two of the four GTR cases had evaluable images for preoperative hypothalamic involvement. One had Type 0 and another Type I. These were too few for statistical comparisons. We had no surgical mortalities, even with reoperations. Surgical mortality was defined as any death within 30 days post operatively. One case of post-operative blindness operated in year 2000 occurred and one case of new post-operative motor weakness treated earliest in our series in 1995.

Ommaya reservoirs were placed in 21 patients. In the early period these were usually placed stereotactically. Seven stereotactic placements earlier in our series utilizing a locally developed stereotactic device, the Cape Town Stereotactic Pointer (CTSP), which used a rigid tripod frame and co-ordinate system, included one failed stereotactic insertion that converted to direct microsurgical placement. A total of 9 insertions were microsurgical and 6 were endoscopic. The first endoscopic Ommaya reservoir insertion was in 2003.

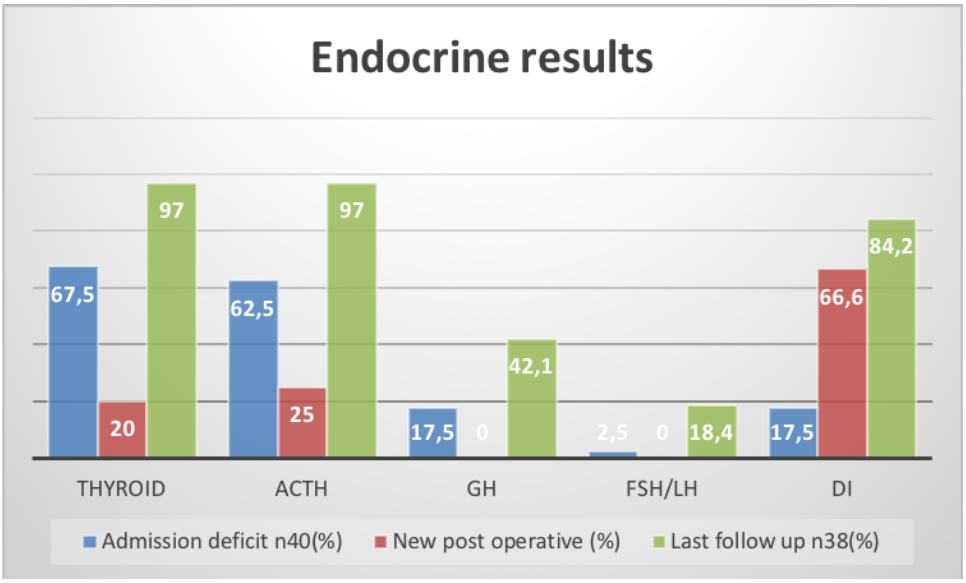
Endoscopic insertions are performed transventricular through the standard coronal midpupillary burr hole with a rigid endoscope. Frameless optical navigation guidance is occasionally used, but cyst perforation is always under direct vision, with adequate enough puncture to allow only the catheter width. A contrast leak test 3 to 6 weeks after insertion is standard practice in our unit.

Technique: Under aseptic technique and local anaesthetic, the Ommaya reservoir is aspirated to a minimum volume equal to the instillation volume. Dilute water soluble contrast is then injected into the reservoir, followed by CT scan. The test is passed if contrast is contained within the cyst wall and failed if there is spillage into the ventricles or subarachnoid space. Failure of leak test requires repeat procedure after another 6 weeks. Eight patients (19.5%) required ventriculo-peritoneal shunts, including one with bilateral catheters. This patient had bilateral shunts in 1998 prior to the introduction of endoscopy.

Endocrine

Table 7 summarises pre and postoperative endocrine findings. One patient had no preoperative endocrine data after initial surgery at an outside institution and another 3 had no long-term post-treatment endocrine data due to not following up at the MDT clinic. Results of 40 preoperative and 38 long-term follow patients are presented. Preoperative DI was diagnosed in 17.5% of cases. Of the 33 patients without preoperative DI, 22(66.6%) developed early post-operative DI. This rate is comparable other series. The overall long-term rate of DI at last follow up, after multimodality treatment and tumour recurrences, was 84.2%, (32 of the 38 patients with available data).

Table 7: Hormonal profile before and after therapy. Three patients did not have adequate follow up data.



Growth and Growth Hormone

Eighteen patients had growth and weight charting available at last follow up. The remainder either had no growth monitoring performed or no record available. Thirteen children had growth failure with age-matched height below the 5th centile; 12 were not on GH supplementation; 4 of 18 were classified as obese. Two patients in the series showed growth without growth hormone, plotting between the 50th- 75th centiles for age/gender. These same patients were however also significantly above the 95th centiles for weight. Four patients received GH supplementation, the earliest administered in 2004. All demonstrated good growth including 1 patient who began well below the 5th centile (figure 2). One patient received replacement for 5 years: However, multiple tumour recurrences prompted a cessation of treatment out of concern for the role of GH in inducing tumour regrowth. This patient demonstrated good growth velocity while on treatment (figure 2a). Among those with GH deficiency, hormonal replacement had a positive effect on growth velocity Figure 2b. Of note, because of the cost incurred with GH supplementation, GH is not easily available to all patients; special motivation is required.

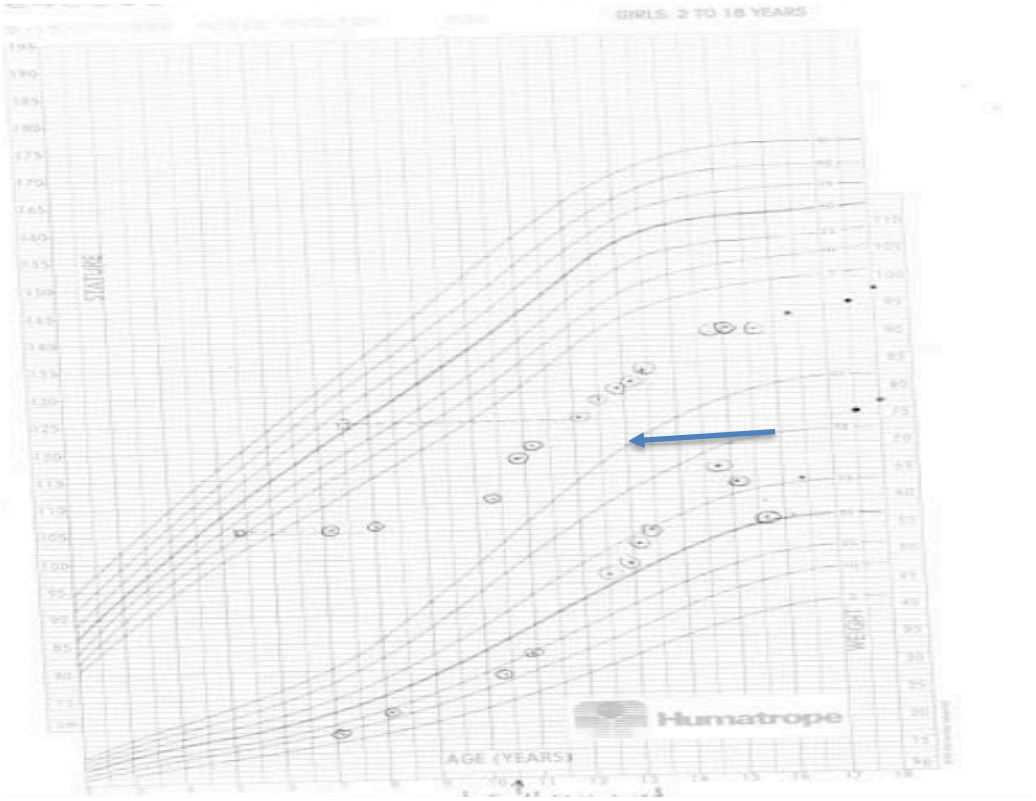


Figure 2: catch up growth on commencement of GH but remains below 5th centile.

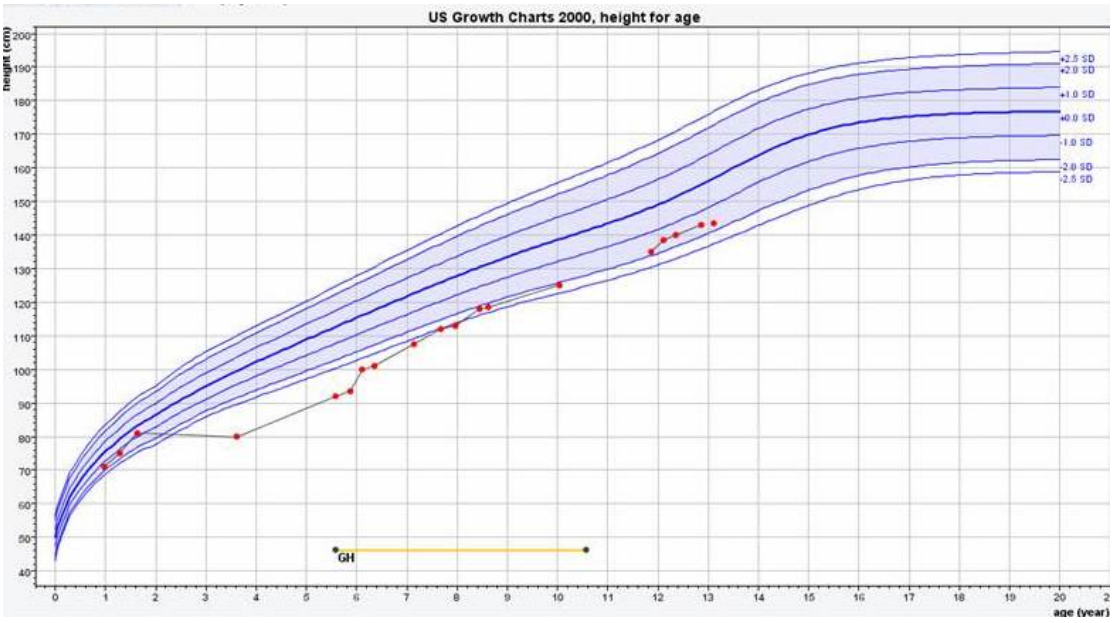


Figure 2a: Growth chart of a patient with GH deficiency, showing initial growth below standard deviations for age and gender. On initiation of GH the chart

shows catch up growth to -1 SD. Cessation of therapy due to recurrent tumour growth leads to plateau of growth curve.

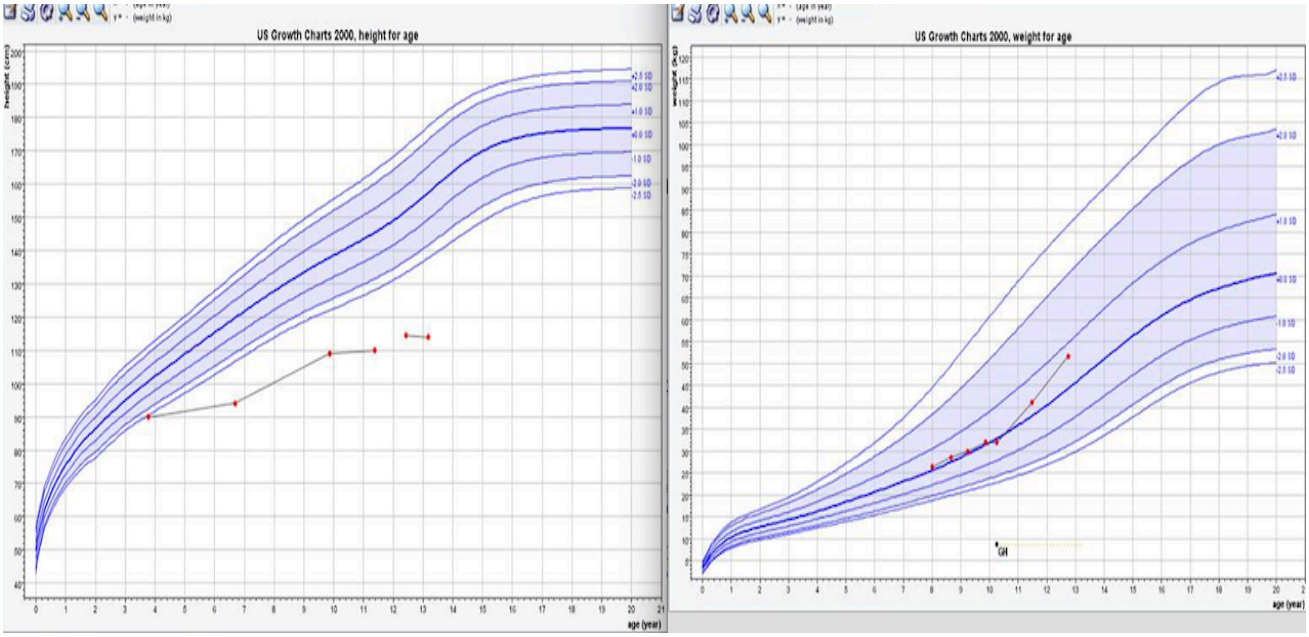


Figure 2b**:** Gender matched comparative charts of growth in two patients with GH deficiency. Left) the chart of a patient with no GH replacement shows velocity significantly below SD for age and gender. Right) the chart of a patient demonstrating increased growth velocity after introduction of GH.

Radiotherapy

A total of 30 patients were treated with post-operative radiation therapy. Of the 11 patients who were not treated, 1 was observed after GTR and subsequently lost to follow up; 1 patient returned to an outside province and also lost to follow up. Two patients had small intrasellar tumours that were observed with no growth; 2 were sent to the referring institution with radiotherapy services but there was no data on treatment there. There were 4 patients with decisions for observation after near total resection, these were recent and still show no progression, and a single patient who only received intracystic interferon with sustained tumour response. All cases received fully fractionated 3D conformal external beam radiotherapy on a Linear Accelerator (LINAC) machine. No patients received radiosurgery. A small number of patients were partially treated with protons, however the inconsistent

availability of such treatment meant that none received exclusive proton therapy for independent analysis. The mean dose was 53.8Gy, mean dose per fraction 1.8Gy; 20(66.6%) were treated as planned adjuvant therapy and 10(33.3%) were treated at tumour recurrence.

The time to disease progression between patients treated with surgery alone vs surgery and planned adjuvant radiotherapy was marginally longer for the planned radiotherapy group. The mean time to progression between surgery only and surgery with planned adjuvant radiotherapy was 39.4 and 46 months respectively. This was most likely subject to selection bias, influenced by extent of surgical resection. Of the four patients who had imaging confirmed GTR, two had follow up data. One recurred at 22 months, the other at 65 months after surgery alone. The two remaining patients did not follow up to the combined clinic. There were 2 early radiotherapy complications, both were transient alopecia, 5(16.6%) had late complications. The latter are listed in table 8.

	Complication	Time from radiotherapy
Patient 1	Seizures	42 months
Patient 2	Vision deterioration	12 months
Patient 3	Transient movement disorder	48 months
	Moyamoya disease	144 months
Patient 4	Seizures	12 months
	Cognitive decline	24 months
Patient 5	GH/ACTH deficiency	15 months

Table 8: radiotherapy complications. These were attributed to radiation if there was documented exclusion of recent surgery, hydrocephalus or disease progression after radiation treatment.

Intracystic Treament

There has been an evolution in our intracystic therapy approach, driven by clinical experience and availability of newer, safer agents. Early in the series we used Yttrium 90. Only a single patient had available data after use of this

agent. This patient treated in 2001 developed late complications of DI and epilepsy, disease control was sustained for 36 months after which tumour cyst recurred.

Six patients were treated with Bleomycin. Of these five had follow up data. Tumour control was modest, lasting 24, 36 and 38 months in three patients. One had complete resolution with no recurrence after Bleomycin was used as salvage therapy 76 months from initial surgery. However one patient suffered severe, fatal hypothalamic injury and prolonged coma after spillage of the agent into the ventricular system. Interferon has been used exclusively since then.

Six cases were treated with interferon. In a single patient, the tumour cyst recurred 8 months after IF therapy. Another patient who received 3MUx5 sessions (less than full course) had sustained cyst control up to the last follow up. This was at first recurrence 5 years after STR and 3 months following adjuvant radiotherapy. A single complication of transient lethargy and somnolence after instillation was noted. This was presumed a complication following spillage of the agent into the ventricular system; however the patient made a complete recovery. Table 9 summarises the patient details. The standard protocol for Interferon at our institution consists of 3MU for 12 sessions, totalling 36MU if tolerated, on an out patient basis. Each instillation is preceded by a minimum of 1.5-2ml aspiration of the reservoir to accommodate the 1ml drug instillation and 1ml flush. The cycle lasts 4 weeks. Interferon is currently the agent of choice at our institution.

	Dose	Time from surgery (months)	Salvage or Planned adjuvant	Cyst Response	Complication
Patient 1	36 MU	103	Salvage	Controlled at 10 months	Nil
Patient 2	36 MU	83	Salvage	Controlled at 34 months	Somnolence Fatigue (transient)
Patient 3	15 MU	62	Salvage	Controlled at 12 months	Nil
Patient 4	36 MU	6	Adjuvant	Recurrence at 8 months	Nil
Patient 5	36 MU	6	Adjuvant	Controlled at 16 months	Nil
Patient 6	36 MU	5	Adjuvant	Controlled at 6 months	Nil

Table 9: a summary of patients treated with interferon alpha along with complications and cyst response at the last follow up period.

Functional outcome

The four-tiered functional outcome scale by Wen (1989)(70) and colleagues was used to evaluate level of function at last follow up. Class I is grossly normal and independent, Class II independent but with panhypopituitarism and mild psychological dysfunction, Class III patients are partially dependent with serious visual impairment, neurological deficits including seizures and learning disabilities. Class IV entirely dependent on others for self-care. All patients are seen at a multidisciplinary clinic including paediatric neurosurgeons, medical and radiation oncologists, educational psychologist and paediatric endocrinologists. At last follow up, 32 were still attending the follow up clinic: 7(21.8%) were Class I, 10(31.2%) Class II, 15(46.8%) Class III. No patients had Class IV function. However, only 13 had educational psychology evaluation reports. Of these, 6 had learning disability and were

not in mainstream school, 4 had normal IQ and were in normal school. Two patients were blind, receiving assisted schooling and one with very poor vision, also in assisted schooling.

There were five deaths in our series and all were late occurrences. Table 10 summarises case mortalities and last documented follow up. All three of the patients who presented in endocrine crisis were from outside of the province and had missed multiple scheduled MDT clinic appointments before representing *in extremis*. While within the care of our system, control of DI and education of caregivers on DDAVP administration was good. Reintegration into the community, which is frequently remote and under resourced resulted in failure of adherence.

Mortality	Time from diagnosis	Class at last F/U	Cause
2002	7y5m	Unknown	Unknown
2001	6y	Class III	Uncontrolled DI
2003	7y4m	Class II	Unknown, unexpected
2005	6y	Class III	Endocrine, DI
2009	8y	Class III	Uncontrolled DI

Table 10: summary of mortalities reflecting severe DI crisis as important contributor to late mortality.

Discussion

Craniopharyngioma is a benign but locally aggressive tumour with a high propensity for recurrence. Recurrences have been associated with higher treatment related morbidity and mortality(71,72). However, although more aggressive surgical resection leads to reduced recurrence, it also leads to higher morbidity. The morbidity incurred by aggressive surgery is attributed to hypothalamic dysfunction from manipulation of the tumour capsule which is often adherent. Vascular injury, especially small perforator vessel disruption to the deep grey nuclei, internal capsule and the optic chiasm also can occur. This has lead to an evolution in management philosophy worldwide. Previously there was greater enthusiasm for aggressive complete resection; more recently a more cautious approach is often adopted, comprising

maximal safe resection and adjuvant radiotherapy in pursuit of better quality of life(4,30,43,49). Overall survival rates have been high - 3, 5 and 10 year survival being 97%, 96% and 93% respectively(51). This has followed improved treatment techniques, therapeutic agents with better side effect profile and advancements in surgical strategies. A few issues remain debated though. For example, some institutions still prefer more aggressive resection, arguing that the endocrinological morbidity can be managed. In this though, the context in which the child is managed is of critical importance, particularly if resource limitations in the environment lead to suboptimal endocrine support. The risks of failures in the system are demonstrated in our results.

In this study, we evaluated our institutional experience with craniopharyngiomas to document evolution in treatment and patient outcomes. In this it is important to keep in mind the age range when comparing results to other series. Ours is predominantly a population of young children and the later peak of 14-16 year olds is missed. While most institutions included patients up to 18-21 years of age, we were limited to <14 due to institutional policy. Controlling for age, the numbers accrued over similar follow up periods (18-22years) were comparable(30,32,66,73). Some of the other differences likely relate to public education, quality of primary care in peripheral communities, referral patterns and late presentation. As the only specialised paediatric centre in the country, patient referrals frequently come from outside of the province, often with prolonged delays between symptom onset and specialist contact. Consequently we expect a higher incidence of large to giant tumours and advanced disease morbidity at presentation. Consistent with other series, headache and visual deterioration are the most frequently reported symptoms in the literature. In a series of 54 children with craniopharyngiomas, Tomita et al reported headaches and visual change in 29 and 18 children respectively(74). Effenterre et al in a larger series of 122 mixed adult and paediatric cases, found 75% of patients to have decreased vision as a presenting complaint(22). Poor vision and headache both accounted for 56% in our series consistent with this trend.
Our data showed a high rate of preoperative hormonal deficits, particularly thyroid and adrenal hormone dysfunction. Preoperative GH was lower than

reported in other series. Muller et al reported a preoperative GH deficiency rate of 75%, with TSH and ACTH rates of 25% each(25). These findings were reversed in our series with higher ACTH, TSH rate 67.5% and lower GH. This is interesting however, considering that 26% of our children had pathological growth at diagnosis, which is in keeping with other institutional experiences. Preoperative DI was seen in 17.5% of patients, higher than generally reported, perhaps reflecting slightly larger volume tumours in our experience.

Tumour volume is a predictor of extent of resection, degree of hypothalamic invasion and quality of life outcomes(28,33,75). In series with similar patient numbers, giant tumours constituted between 0,7% to 24% of the tumours imaged(75–77). Our rate of 32.3% was higher than usually reported. It would be expected that this would influence the rate of complete resection and radiation morbidity, given the larger treatment field that may need coverage. This along with a 45% incidence of hypothalamic invasion likely influenced the high STR rate. Unlike other centres, which have gone through periods of aggressive surgery and more cautious STR with RT, we have adopted a view of maximal safe resection followed by either surveillance or adjuvant radiotherapy. Similarly with our approach to insertion of Ommaya catheters, a retrospective series from Brazil found a comparable rate of complications independent of technique used for insertion(78). Over the years, our service has evolved away from frame-based stereotactic placement, to endoscopic placement of catheters.

This evolution with improved technology and data availability is most apparent with the appreciation for the role of radiation therapy in achieving durable tumour control in subtotally resected tumours with a favourable side effect profile. Missing radiotherapy after subtotal resection emerged as a risk factor for early recurrence or progression(34,49,50,79–81). Improved planning and dose delivery technologies have helped improve long-term side effect profile. Charged particle therapy, usually protons has been suggested as a further improvement with favourable radiobiological profile for paediatric brain tumours(41,82). Although some of our patients received partial treatment with protons, none completed treatment without photon-based therapy, so no

meaningful assessment can be made on the efficacy. Our side effect profile was low with only single cases of visual deterioration, cognitive decline and moyamoya disease, which was diagnosed on imaging but was asymptomatic. Delayed progressive hormonal loss is a well-known complication of radiation therapy. Growth hormone is most frequently affected, even at doses as low as 18Gy, this can be as high as 50%-100%(83). We had one patient with such a complication, occurring at 15 months after receiving a dose of 54Gy in 1,8Gy/fraction. Pre-radiation hormonal deficiencies are far more common however.

In terms of intracystic treatments, we have evolved from Beta emitting isotopes (Yttrium 90) to Bleomycin, to Interferon Alpha. Consistent with emerging international results, we have found interferon to have a safer profile and tumour cyst control rates have not been inferior. The issue of what to do with planned Interferon instillation if there is contrast leakage from the cyst is an unresolved issue. Anecdotally, others have not reported significant side effects; however, we have been cautious because of our experience with one patient as described above.

Endocrine

An important outcome of our study is the significant role that endocrine dysfunction plays in the quality of life and survival of craniopharyngioma patients in the developing world setting. Our results raise health economic and health coverage issues. It emphasizes the necessity of multidisciplinarity and the need for endocrine surveillance, particularly when patients are from rural areas. Panhypopituitarism is the most common morbidity among craniopharyngioma survivors(84). This correlates with a minimum of Class II Wen functional grade. Thyroid and adrenocortical replacement is widely available in South Africa but growth hormone is restricted due to cost. Significant motivation by paediatric endocrinology is required to have the agent available. Of our charted patients, a significant proportion were markedly growth restricted while objectively documented to be GH deficient. Equally, the positive effect of replacement on the height gain is evident in our data. Another indirect possible benefit of GH supplementation is on the

distribution of body fat. Obesity is a frequent consequence of disease and therapy, while cardiovascular related events are important contributors to late mortality and morbidity(66,67,85,86). GH is known to reduce total body fat, while this has not been correlated with reduced cardiovascular events, it may be of benefit against the likelihood of obesity in this group.

Diabetes insipidus has accounted for all of the known cause mortalities in our series. Up to now, little tumour directed intervention has significantly reduced the incidence of this morbidity and the long-term risk remains high. The difficulty is when patients are referred for specialised treatments from remote centres and provinces without the ability to sustain the same standard of care or quality of surveillance. Patients may not be able to afford transport to a major centre for ongoing surveillance and/or may neglect to do so if the child is looking well. An additional difficulty is the multi-lingual culture in South Africa, often without equivalent words for specific medical terms. There is difficulty in communicating the meaning and importance of a hormone in some South African languages. Whether this is a contributor to the inability to sustain compliance with life sustaining hormonal replacement like DDAVP is uncertain but possible. Further work is required to determine the reasons for poor follow up in the patients who died.

Limitations

As a retrospective study, poor record keeping, incomplete data and medical records that were destroyed by hospital administration for inactive patients limited us. The latter has important considerations for long term chronic care management of patients, research and medicolegal concerns. Over a long period of time, we expect that several changes are likely made for treatment regimes, so comparisons of outcomes between patients early and late in the series are not straightforward. The age limit excluded adolescents who might express different clinical behaviour; this also limited the sample size and reduces comparability to other series. The outcomes also reflect a specialised centre with a small number of dedicated and experienced clinicians, which may not be generalizable to other centres. Limited data were available to

determine the precise conditions in which the late deaths occurred; therefore important contributing factors can only be surmised.

Conclusion

The current study shows the complexity and heterogeneity of patients with craniopharyngioma, which requires multidisciplinary and individualised approaches to management. An evolution in approach and willingness to adopt newer modalities has allowed our results to be comparable to more resourced environments. Surgical morbidity and mortality is low and overall survival high with a cluster in the mild to moderate quality of life survival scores. Radiation therapy has proven to be safe and effective with low complication rates. Although our numbers were not large enough to clarify efficacy between planned adjuvant and salvage treatment timing. The local landscape of centralised care and risk of loss to follow up probably supports planned adjuvant fractionated radiation therapy to patients with residual solid tumour. However, the late deaths in our series highlight an important aspect of long-term care. Access to regular surveillance with endocrinological support, education of the family, and engagement with local health care providers are all critical factors that need greater attention if we are to avoid late morbidity and mortality. A further challenge is the limited availability of growth hormone in the public hospitals and the influence that this restriction has on adequate growth and development, as demonstrated in our series. It seems imperative that this drug be made available to children who demonstrate GH deficiency or growth restriction. Prescribing restricted to endocrinologists is a simple intervention to control cost.

More than anything, our results again show the critical role of a multi-disciplinary team approach to treatment of children with brain tumours. The value of this in our estimation is arguably greater than access to any specific new tools or therapies. Just as important, our results emphasize that childhood brain tumours and the consequences of treatment require a long term, chronic care approach that goes well beyond the acute cluster of therapies in the acute phase.

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