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SUPPLEMENT ARTICLE

SIOP PODC–adapted treatment guidelines for craniopharyngioma in low- and middle-income settings

Nisreen Amayiri[1] | Ariane Spitaels[2,*] | Mohamed Zaghloul[3,*] | Anthony Figaji[4,*] | Sergio Cavalheiro[5,6] | Hermann L. Muller[7] | Moawia Elhassan[8] | Jeannette Parkes[9] | Naureen Mushtaq[10] | Mohamed El Beltagy[11] | Yacoub A. Yousef[12] | Natia Esiashvili[13] | Michael Sullivan[14] | Marcos Devanir da Costa[5,6] | Patricia Dastoli[5] | Fatima Mubarak[15] | Ute Bartels[16] | Omar Chamdine[17] | Alan Davidson[18] | Awni Musharbash[19] | Patricia Alcasabas[20] | Eric Bouffet[16,*] | Simon Bailey[21,*]

[1] Pediatric Oncology Department, King Hussein Cancer Center, Amman, Jordan

[2] Division of Endocrinology, Department of Pediatric Medicine, Faculty of Health Sciences, UCT, Cape Town, South Africa

[3] Radiation Oncology Department, National Cancer InstituteCairo University and Children's Cancer Hospital, Cairo, Egypt

[4] Department of Neurosurgery, Red Cross War Memorial Children's Hospital and University of Cape Town, Cape Town, South Africa

[5] Division of Neurosurgery, Pediatric Oncology Institute/GRAACC, Universidade Federal de São Paulo, Sao Paulo, Brazil

[6] Department of Neurology and Neurosurgery, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, Brazil

[7] Department of Pediatrics and Pediatric Hematology/Oncology, University Children's Hospital, Klinikum Oldenburg AöR, Oldenburg, Germany

[8] Clinical Oncology department, National Cancer InstituteUniversity of Gezira, Wad Madani, Sudan

[9] Department of Radiation Oncology, University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa

[10] Department of Pediatric Hematology and Oncology, Aga Khan University Hospital, Karachi, Pakistan

[11] Department of Neurosurgery, Kasr Al-Ainy School of Medicine, Children's Cancer Hospital Egypt, Cairo University, Cairo, Egypt

[12] Ophthalmology division/ Surgery department, King Hussein Cancer Center, Amman, Jordan

[13] Radiation Oncology Department, Winship Cancer InstituteEmory University, Atlanta, Georgia

[14] Department of Pediatric Hematology and Oncology, Royal Hospital for Sick Children, Melbourne, Victoria, Australia

[15] Radiology Department, Aga Khan University, Karachi, Pakistan

[16] Division of Hematology/Oncology, Hospital for Sick Children, Toronto, Canada

[17] Department of Pediatric Hematology Oncology and stem cell transplantation, King Fahad Specialist Hospital, Dammam, Saudi Arabia

[18] Hematology-Oncology Service, Red Cross Children's Hospital, Department of Pediatrics and Child Health, University of Cape Town, Cape Town, South Africa

[19] Neurosurgery division/Surgery department, King Hussein Cancer Center, Amman, Jordan

[20] University of the Philippines-Philippine General Hospital, Manila, the Philippines

[21] Department of Pediatric Oncology, Great North Children's Hospital, Newcastle upon Tyne, UK

Abbreviations: ACTH, adrenocorticotropic hormone; ADH, antidiuretic hormone; CRT, conformal radiotherapy; CT, computerized tomography; CTV, clinical tumor volume; DDAVP, desmopressin; DI, diabetes insipidus; EFS, event-free survival; GTR, gross tumor resection; GTV, gross tumor volume; HIC, high-income countries; INF, interferon; K, potassium; LIC, low-income countries; LIMC, low middle-income countries; MDC, multidisciplinary clinic; MRI, magnetic resonance imaging; Na, sodium; NTR, near total resection; OS, overall survival; PICU, pediatric intensive care unit; PODC, pediatric oncology in developing countries; PTV, planning tumor volume; QoL, quality of life; SIADH, syndrome of inappropriate antidiuretic hormone secretion; SIOP, International Society of Pediatric Oncology; STR, subtotal resection; T4, thyroid hormone; VMAT, volumetric modulated arc therapy; WHO EML/ EMLc, The World Health Organization Essential Medicines List and Essential Medicines List for Children

Correspondence
Simon Bailey, Great North Children's Hospital, Newcastle upon Tyne, United Kingdom.
Email: simon.bailey@ncl.ac.uk

*A.S., M.Z., and A.F. contributed equally to this article.

Eric Bouffet and Simon Bailey had equal contribution as senior author.

Abstract

Pediatric craniopharyngioma is a rare tumor with excellent survival but significant long-term morbidities due to the loco-regional tumor growth or secondary to its treatment. Visual impairment, panhypopituitarism, hypothalamic damage, and behavioral changes are among the main challenges. This tumor should be managed under the care of a multidisciplinary team to determine the optimum treatment within the available resources. This is particularly important for low middle-income countries where resources are variable. This report provides risk-stratified management guidelines for children diagnosed with craniopharyngioma in a resource-limited setting.

KEYWORDS
adapted guidelines, craniopharyngioma, LMIC, SIOP PODC

1 | INTRODUCTION

Craniopharyngioma constitutes < 5% of pediatric intracranial tumors.[1] Although survival in high-income countries (HIC) is in the range of 84%-95% at 20 years,[2] this comes at the cost of significant morbidity due to the locoregional tumor effects or secondary to treatment.[3,4] Children are often left with visual impairment, panhypopituitarism, hypothalamic damage, and behavioral changes proportionate to the degree of tumor aggressiveness or the treatment given.

The surgical approach is dependent on a number of factors including tumor size and location, degree of hypothalamic involvement, and availability of resources and expertise. In a HIC multicenter study, three-year event-free survival (EFS) of 67% after gross total resection (GTR) was reported[5] compared with 23% after subtotal resection (STR). In HIC, the balance of GTR versus preservation of hypothalamic function has more recently moved toward the latter,[6-8] due to the long-term consequences of hypothalamic damage. The morbidity of aggressive surgery has meant that many institutions now favor conservative resection followed by radiotherapy. This approach is associated with a 70%-90% EFS[9,10] and better long-term quality of life (QoL), mainly due to reduced incidence of hypothalamic damage.[11-13] A prospective multicentric German trial comparing limited surgery with and without postoperative radiotherapy showed 88% lower risk of recurrence/progression with radiotherapy compared with surgery alone ($P < 0.001$).[14] Although there has been debate whether radiotherapy should be given immediately post incomplete resection, the prospective trial Kraniopharyngeom 2007 evaluating delayed radiotherapy following STR did not reveal inferior outcomes (Mueller, Personal Communication).[11,15]

For predominantly cystic lesions, instillation of intracystic interferon (INF) has been reported to be effective in avoiding or delaying radiotherapy.[16-18] However, this does not demonstrate that any of these approaches are preferable treatment options in low middle-income countries (LMIC) as the most important factor in the treatment of this nonmalignant tumor is the long-term morbidity that is produced, which in turn has the largest effect on longevity and QoL.

The burden of treating pediatric craniopharyngioma in LMIC is difficult to assess as only few reports have been published; in some papers, children are included among adult series[19] or studies only focus on recurrences.[20] Other reports elaborate on the clinicomorphological presentation[21] or surgical approaches[22] without description of associated morbidities. High postoperative mortality (32%) has been reported in a Nigerian paper[23] but has not been observed in series from Turkey,[24] Jordan,[25] and Egypt.[22] In the Jordanian experience,[1] the five-year overall survival (OS) was 87% ± 7%, similar to HIC. However, QoL of surviving children was of concern with difficulties in school and community integration due to associated morbidities. The authors identified delayed presentation, late referrals after initial surgery by teams with limited expertise in pediatric craniopharyngioma, and limited community rehabilitation resources as the main causes of increased morbidity.

Management of craniopharyngioma is complex and a multidisciplinary team (MDT) approach is helpful to assess the consequences of differing treatment approaches. The goal of treatment is to treat life/function-threatening conditions, and to achieve effective tumor control while balancing the risks of different treatments depending on the facilities and expertise in any one unit. Because LMIC units are less likely to have the full complement of HIC MDT members (e.g., pediatric neurosurgeons, pediatric and radiation oncologists, pediatric endocrinologists), may have limited facilities (intraoperative equipment and radiation machines), and may lack supportive services (psychologists, social workers, school integration services), this guidance document is stratified according to the resources of individual units.

2 | SIOP PODC RECOMMENDATIONS

The International Society of Pediatric Oncology (SIOP) has a Pediatric Oncology in Developing Countries (PODC) committee that produces recommendations for the management of childhood cancers in LMIC as defined by the World Bank. This includes guidelines for

implementation and for continuous quality improvement based on local outcome data. Service levels describing facilities and personnel required for the care of patients with craniopharyngioma are defined in Table 1. Setting 1 is defined as meeting the minimal requirements for the treatment of pediatric craniopharyngioma.

3 | METHODS

A multidisciplinary group of neurosurgeons, radiation and pediatric oncologists, radiologists, pediatric endocrinologists, and an ophthalmologist with experience in managing children with craniopharyngioma in LMIC setting was formed. Online meetings were hosted via the Cure4Kids website (www.cure4kids.org), and minutes were taken. Specialists in a specific field, e.g., radiotherapy (both from LMIC and HIC) were asked to write their part of the guidelines. The final draft of the guidelines was circulated to all group members, and comments were integrated in the paper.

The World Health Organization Essential Medicines List and Essential Medicines List for Children (WHO EML/EMLc) have been used as references for the minimum hormonal treatment that should be available in a LMIC.[26] The WHO Model List of Essential In Vitro Diagnostics First edition (2018) does not include any hormonal tests, but does include serum and urine electrolytes.[26] Recommendations then were discussed at SIOP PODC meetings, and guidelines were ratified by the SIOP board.

4 | DIAGNOSIS OF CRANIOPHARYNGIOMA

4.1 | Clinical presentation and pathology

Craniopharyngiomas are benign neoplasms of the sellar, supra, and parasellar region. Main presenting signs and symptoms are those of raised intracranial pressure such as headache and vomiting, visual impairment, and hormonal deficiencies, e.g., growth failure, obesity, delayed or precocious puberty, or polydipsia/polyuria. Most patients present with endocrine deficits, growth hormone deficiency being the most common one.[1] Duration of symptoms is often months or even years.

There are two main histopathological subtypes: the adamantinomatous type is most common in children whereas the papillary type is mostly seen in adults. Adamantinomatous craniopharyngiomas are characterized by multilobulated dense nodules and trabeculae of squamous epithelium outlined by columnar epithelium. They are usually invasive, calcified and adherent to underlying tissues. Both craniopharyngioma subtypes are considered standard diagnoses in the hands of pathologists even with limited experience in pediatric brain tumors, using light microscopy and H&E staining. Surgical aspiration of oily cystic content is a surrogate of diagnosis and histological confirmation in this context would not be required.

4.2 | Radiology

On computerized tomography (CT) scan, adamantinomatous craniopharyngiomas are most often cystic (90%) with/without a solid component, and 90% show calcifications and enhancement. The pattern of enhancement is nodular in solid lesions and rim-like in cystic lesions. On magnetic resonance imaging (MRI), cysts are variably hyperintense on T1/T2 due to high protein content while solid components appear nodular.[27,28] Papillary craniopharyngiomas are usually solid and rarely calcified. It is important to assess whether the hypothalamus is displaced or involved by the tumor as this is integral to the surgical approach and to subsequent morbidity.[29] In LMIC, tumors may be larger due to delayed presentation.[24,25]

The main radiological differential diagnoses include hypothalamic/chiasmatic low-grade glioma (usually solid or contains small cystic/necrotic components, calcifications are rare, and avid enhancement is common) and suprasellar germ cell tumor (usually solid, calcifications are rare, blood and cerebrospinal fluid [CSF] markers may help). Ideally, both CT scan and MRI (T1/T2/flair sequences) are useful for diagnosis and for surgical planning (Supporting Information Figures S1-S3).

4.3 | Visual assessment

As part of the management, it is essential to assess visual acuity, color vision, visual field, and optic nerve disks. Visual acuity can be assessed by different methods depending on age and/or cognitive ability.[30] Teller Acuity Card and Lea Chart are used for subjects ≤4 years old,[31] and Allen or Snellen optotypes for older patients.[32] Normal acuity is assumed to be 0.0 logMAR (20/20), and significant change is defined at least a two-line difference between visits. Color vision can be assessed by the Ishihara test in children > 3-years old, and visual field in a child > 5-6 years old. Fundoscopy should ideally be performed by an ophthalmologist to document edema, pallor, and/or atrophy.

4.4 | Hormonal assessment

More than 80% of children have pituitary hormone deficits at diagnosis, with further deficits occurring during or after treatment.[33] Wherever possible, recommended investigations and care for each hypothalamic-pituitary dependent hormone deficiency should be followed.[34-44] A child or teenager with a craniopharyngioma should be questioned and carefully examined for features of growth hormone deficiency (height and weight, ideally on a growth chart),[40-42,45-48] diabetes insipidus (polyuria/polydipsia),[38,39] hypothyroidism,[35-37] hypocortisolaemia, secondary sexual characteristics (Tanner staging),[43,44,49] obesity and features of hypothalamic dysfunction (sleep disturbances, behavioral changes, school performance).[33,50] Table 3 summarizes the assessment of hormonal deficiencies and management in craniopharyngioma.

TABLE 1 Infrastructural and personnel service line levels for the selection of SIOP PODC-adapted treatment regimens for craniopharyngioma. Level 1 is the minimal requirement for treating children with craniopharyngioma

Service	Level 0	Level 1	Level 2	Level 3	Level 4
Pediatric cancer unit description (multidisciplinary team operates at all levels)	Pilot project	Some basic oncology services	Established pediatric oncology program with most basic services and a few state-of-the-art services	Pediatric oncology program with all essential services and most state-of-the-art services	Pediatric oncology center of excellence with all state-of-the-art services and some highly specialized services (e.g. proton beam radiation therapy)
Typical settings	LIC in disadvantaged areas	LIC in larger healthcare centers, lower MIC in disadvantaged areas	Lower MIC in larger healthcare centers, upper MIC in disadvantaged areas	Upper MIC in larger healthcare centers, most centers in HIC	Selected tertiary and quaternary care centers in HIC
Diagnosis, staging, and therapeutic capabilities					
Pathology	None	Aspiration of cystic fluid (motor oil like content)	Microscope, H&E staining, CSF cytology Limited IHC panel (disease-specific), Cytospin for CSF samples	Complete IHC, molecular pathology for most diseases	Research diagnostics, whole-genome sequencing, molecular pathology for all diseases
Diagnostic imaging	None	Radiographs, ultrasound	CT scan	MRI PET-CT may be available	Specialized imaging; advanced nuclear medicine applications
Medications availability			Access to hormone replacement therapy	Access to hormone replacement therapy and intracystic INF	Access to hormone replacement therapy and intracystic INF as well as early-phase agents
Radiation therapy facilities	None	Cobalt source; 2D planning	Cobalt source or Linear accelerator; 2D or some 3D planning. Ability to deliver treatment on at least four days per week.	Linear accelerator; Full CRT. IMRT frequently available	IMRT. Proton beam facility
Personnel					
Surgery and surgical subspecialties relevant for each cancer	No surgeon	General surgeon or adult subspecialty surgeon (neurosurgeon, ophthalmologist, other)	Pediatric neurosurgeon with some experience of craniopharyngioma surgery	Pediatric neurosurgeon with extensive experience of craniopharyngioma surgery	Pediatric neurosurgical team with extensive experience of craniopharyngioma surgery
Pathology	No pathologist	Pathologist available for some cases	Pathologist available for all cases	Hemato-pathologist and pediatric pathologist available	Pathologist with highly specialized disease-specific expertise
Radiation therapy	None	Radiation therapists with adult expertise	Radiation therapists with some pediatric experience	Radiation therapists with pediatric expertise	Pediatric radiation oncologist with highly specialized disease-specific expertise

Abbreviations: CSF, cerebrospinal fluid; CRT, conformal radiotherapy; H&E, hematoxylin and eosin; HIC, high-income countries; ICU, intensive care unit; IHC, immunohistochemistry; IMRT, Intensity-modulated radiotherapy; INF, interferon; LIC, low-income countries; MIC, middle-income countries; MRI, magnetic resonance imaging; PET-CT, positron emission tomography–computed tomography.

TABLE 2 The minimum initial assessment of children with craniopharyngioma

	Findings that must be evaluated
Clinical history	• Symptoms of increased intracranial pressure • Visual symptoms • Symptoms of hormonal deficiency (polyuria/polydipsia, short stature/obesity/delayed or precious puberty/hypothyroidism • Fluid intake /urine output • Sleep issues/personality changes/ school challenges • Changes in appetite
Physical examination	• Weight/ height / body mass index (BMI) plotted on growth charts • Pubertal stage (Tanner) • Visual acuity /visual fields /color vision/fundus exam
Complementary exams	• Serum sodium and urea • Urine-specific gravity (if serum sodium is high) • Thyroid hormone level (T4) • Morning cortisol level (if available) • Brain computed tomography (CT) scan (calcifications) • Magnetic resonance imaging (MRI) brain (suprasellar mixed solid cystic mass, relationship to chiasm, pituitary, and hypothalamic involvement)

5 | TREATMENT OF PEDIATRIC CRANIOPHARYNGIOMA IN LMIC

Decisions about the optimal treatment approach for craniopharyngioma in resource-limited environments are influenced by the availability of the following resources: experience and skills of the neurosurgeon, preoperative imaging, operating microscope and surgical instruments, neuroendoscopy, pediatric intensive care unit (PICU), reservoir catheters and intracystic treatments (INF alpha), radiotherapy facilities and expertise, rehabilitation services, long-term endocrine management, neuropsychological support, and special educational services. Patients should be managed through MDT discussions to decide on the best treatment approach including the possibility of referral to a hospital with more expertise in treating this rare tumor. Table 2 shows the general approach to diagnosis, and Figure 1 shows the general consensus on treatment.

5.1 | Surgery

Initial urgent surgical intervention for life-threatening or immediate vision-threatening lesions should be considered. This may involve a CSF diversion procedure such as a ventriculoperitoneal shunt or an external ventricular drain or urgent decompression of a tumor cyst (an Ommaya or Rickham reservoir may be inserted at this point). Maximum "safe" resection avoiding (additional) morbidities, in particular hypothalamic damage, is the main goal of initial management. Craniopharyngioma surgery is one of the most challenging neurosurgical procedures for several reasons: resection of the tumor from its attachments requires considerable experience, tumors present in a variety of sizes, and may expand in different directions, each of which may require a different operative corridor, and the benefits of resection are a fine balance between surgical skills, patient morbidity, and availability of supportive treatments.

The majority of craniopharyngiomas can be resected through keyhole approaches, which minimize morbidity associated with large incisions. These include subfrontal transbrow, minipterional, transsphenoidal, or interhemispheric approaches, depending on the size and orientation of the tumor, and assisted by endoscopy where needed. In many cases, reasonable debulking in order to decompress the optic apparatus and minimize the field of radiotherapy is adequate. Apart from the general risks of surgery, specific risks include injury to visual pathways, vascular structures (carotid, anterior cerebral arteries, cavernous sinus), brainstem, and hypothalamus/pituitary axis. With proper technique, visual deficits and vascular injury should be rare; however, hypothalamic and pituitary stalk deficits are more common. Surgical planning depends on the condition of the patient and the size, orientation, and nature of the tumor (solid, solid/cystic, or predominantly cystic).

- **Management of hydrocephalus**: Hydrocephalus on presentation may resolve with debulking of the tumor or cyst decompression, but occasionally it requires placement of a ventriculoperitoneal shunt. Although the foramen of Monro is often blocked on both sides, usual practice is to perform an endoscopic septostomy to enable drainage with a single catheter.
- **Management of tumor cysts**: Predominantly cystic craniopharyngiomas (or cystic enlargement postradiotherapy) can be treated with endoscopic or open placement of a catheter connected to a subcutaneous reservoir (Ommaya or Rickham reservoir) if it is a simple cyst. The reservoir may be used to serially drain the cyst and/or to instill intracystic agents to treat the tumor. Multicystic tumors may not be amenable to catheter insertion and would need surgical intervention; however, in some cases drainage of the largest cyst may be useful to relieve pressure or vision-threatening symptoms.

5.1.1 | Possible limitations in LMIC

There are some additional factors that must be considered when deciding on the optimal treatment for children with craniopharyngioma in a resource-limited setting:

- Patients often present later than in HIC; therefore, tumors may be larger and surgically more challenging.

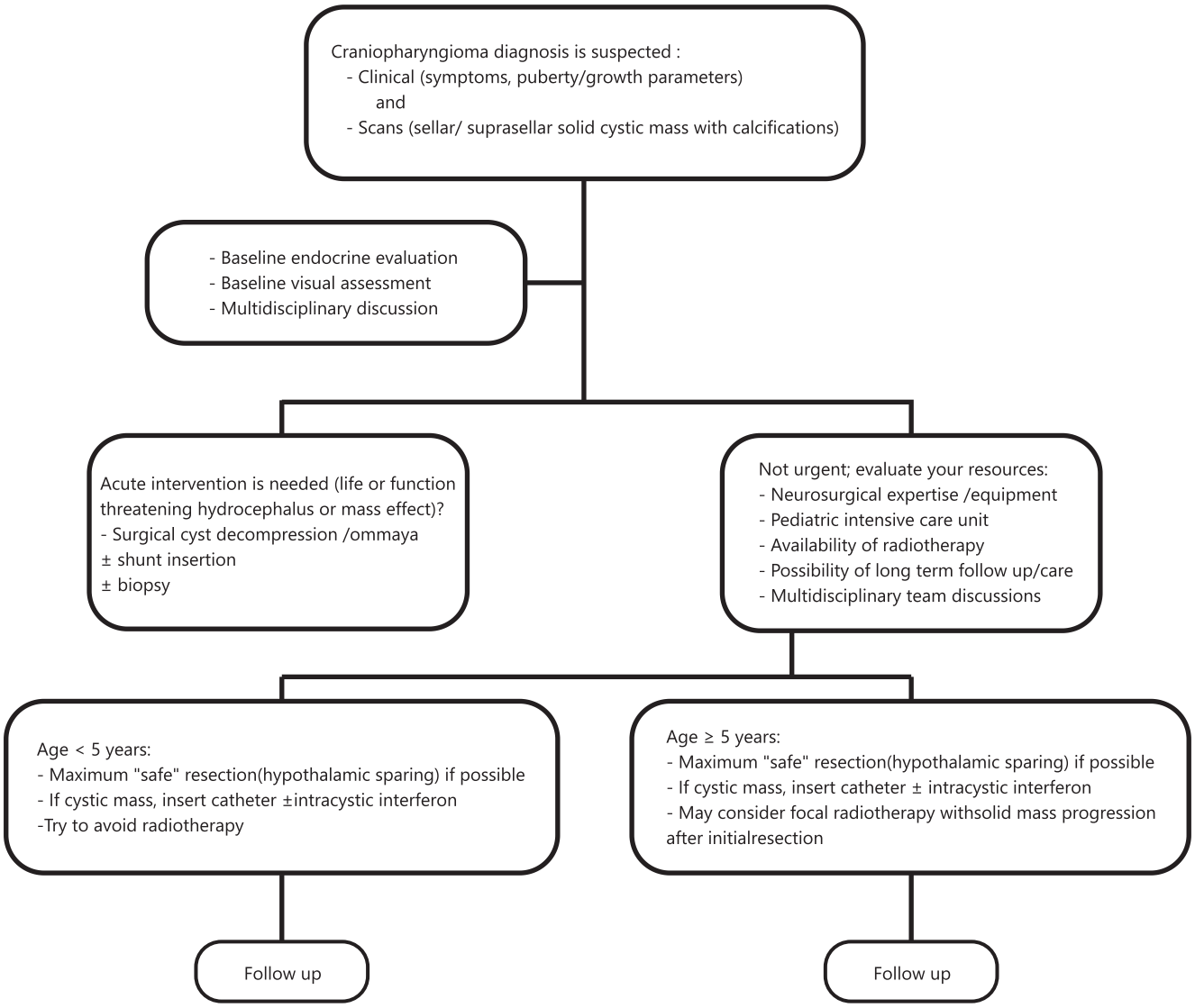

FIGURE 1 General treatment approach in managing children with craniopharyngioma

- Not all countries have experienced neurosurgeons. Where available, neurosurgeons are less likely to be pediatric neurosurgeons. Their experience with craniopharyngiomas may be limited.
- Good surgery requires optimal preoperative imaging and good surgical equipment.
- Presence of PICU or ICU with experience to deal with potential perioperative complications is desirable.
- Neuroendoscopy is useful for placing reservoir catheters into cysts. Expertise and the required equipment may not be available.
- More aggressive surgery minimizes residual tumor but also increases risk. In particular, management of endocrine deficits is key. Poor follow-up and limited access to medications may lead to morbidity and death. Similar principles apply to neuropsychological and education support.

5.1.2 | Perioperative hormonal management

Healthcare professionals responsible for endocrine care should ideally have some experience in the care of children and adolescents in general, and/or have access to advice from a pediatrician or pediatric endocrinologist.

The minimum endocrine tests needed before initial surgical intervention include serum sodium and urea levels, T4, and (if available) early-morning cortisol level. Tables 3 and 4 describe how to diagnose and manage hormonal deficiencies.

If laboratory tests are not available, and surgery is urgently needed:

1. Assume cortisol deficiency secondary to adrenocorticotropic hormone deficiency and give stress doses (Table 4) of

TABLE 3 Assessment of hormonal deficiencies and management in craniopharyngioma

	Clinical assessment (pre and postoperative)	Laboratory diagnosis (pre- and postoperative)	Management	Monitor 3-6 monthly	Other	Resource
ACTH-Cortisol deficiency	Symptoms	- Morning cortisol (07h00-09h00) - Inadequate cortisol level taken during hypoglycemia or illness stress (< 450 nmol/L) - If available, an ACTH stimulation is performed when clinical symptoms indicate deficiencies	*Hydrocortisone*	Symptoms Dose by body surface area	- Triple the dose if unwell (stress dose) - Anti-epileptics increase the metabolism of hydrocortisone, so the hydrocortisone dose may need to increase	34
TSH-Thyroid hormone deficiency	Symptoms	Free or total T4 Not necessary to do TSH	*Levothyroxine*	Free or total T4		35-37
GH deficiency	Growth charts—height trajectory deviates progressively further from normal range *See note regarding "growth without growth hormone"*	For GH-1 (stimulation: IGF-1 (somatomedin) *when well*, repeat in 6months • Inappropriately low GH level *during* hypoglycemia • Stimulation testing Random GH level is not useful	*Somatropin*	Growth (WHO or local growth charts) IGF1 to avoid excessive dosing – maintain in middle range of normal for age and puberty	When to start:As soon as the tumor has been treated and the patient is well[a] Would not delay therapy if stimulation testing is not available	40-42
LH-/ FSH-Sex steroid deficiency	Pubertal status Breast development at latest 13-y girls Testicular enlargement (> 2.5 cm length) by 14-y boys *Do not delay replacement beyond these ages if possible*	• LH • FSH • Estradiol or Testosterone	Estrogen/ testosterone	Secondary sexual characteristics	Discuss (lack of) fertility	43-45
ADH hormone deficiency (diabetes insipidus)	Polyuria and polydipsia Documented intake and output (thirst and polyuria) *Beware of hypodipsia with hypothalamic involvement*	• Serum sodium • Paired urine + serum osmolality Normal serum sodium does not exclude DI in a child with intact thirst who is able to drink independently	DDAVP • Nasal solution • Nasal spray • Tablets	Symptoms		38-39

Abbreviations: ADH, antidiuretic hormone; ACTH, adrenocorticotropic hormone; DDAVP, desmopressin; FSH, follicle stimulating hormone; GH, growth hormone; IGF-1, Insulin-like growth factor; LH, luteinizing hormone; TSH, thyroid stimulating hormone; WHO, World Health Organization.

[a]Traditionally, GH replacement starts one year after any brain tumor is treated, due to the fear of "growing" an active tumor. For craniopharyngioma, some units do not wait (47), as there is no evidence that GH treatment increases progression or recurrence of the tumor (45, 48), and a child may lose height potential, particularly if further treatment of the tumor is needed. Given that one-year recurrence rates are between 16% and 24% depending on the initial treatment modality (46), this initial loss of height potential is of concern, particularly if there is further deferment of GH replacement. There is no evidence that GH replacement within the first year of diagnosis and treatment of craniopharyngioma does increase recurrence or progression of the tumor.

hydrocortisone (or available alternative) at induction of anesthesia and after surgery for 48 hours.[34,38]

2. Consider thyroid hormone replacement if symptomatic[35] (severe hypothyroidism may affect anesthesia and recovery). Do not start thyroid hormone therapy without establishing cortisol sufficiency first. Alternatively, treat for presumed cortisol insufficiency for 48 hours before starting thyroid hormone replacement.
3. Manage diabetes insipidus (DI) preoperatively if it is present[38] and be aware of adipsic DI (Table 4). Allow free access to water until desmopressin (DDAVP) is started. Be aware that DI is "unmasked" by corticosteroid and/or thyroid replacement and IV hydration.

TABLE 4 Core recommendations for hormonal substitution according to hormones listed in the WHO EML/EMLc

A. Management of ACTH-cortisol deficiency		
▷ Minimum laboratory diagnosis: • Morning (07h00-09h00) cortisol—interpret with pediatric reference range if possible, if < lower limit of normal range: assume deficiency, if > upper limit of normal range: assume sufficient, if within the reference range: treat with stress dose when needed. • Inadequate level (below 450 mmol/l) during hypoglycemia or other physical stress If the patient is on basal hydrocortisone replacement, this should be omitted for at least 24 hours before testing. If high doses of corticosteroids have been given for an extended period before the test, a low level of cortisol may be due to suppression of the hypothalamic-pituitary-adrenal axis. The child should continue treatment, but the diagnosis of ACTH deficiency/hypocortisolism should be reviewed over time. * Early morning = 06h00 or as early as possible * *Body surface area* = $\sqrt{(\frac{\text{weight in kg} \times \text{length in cm}}{3600})}$		
	Stress dose for 48 h	Maintenance dose
Hydrocortisone	30-50 mg/m^2/day illness (infuse or 4 × 6 hourly) 100 mg/m^2/day major surgery/sepsis (as above) 50 mg/m^2/day 30-60 minutes before induction and six hourly/by continuous infusion	8-12 mg/m^2 ½-ij-ij of total dose at 06h00 (or earlier), 14h00, 18h00
Alternatives if HC not available (SAMF)[a]		
Prednisone *(not on WHO EML)*	1 mg = 4 mg hydrocortisone Oral	2-3 mg/m^2 Daily (early morning)[a]
Prednisolone	1 mg = 4 mg hydrocortisone Oral liquid: 5 mg/mL [c] Tablet: 5 mg; 25 mg Oral	2-3 mg/m^2 Daily (early morning)[a]
Methylprednisolone	1 mg = 5 mg hydrocortisone Injection: 40 mg/mL (as sodium succinate) in 1-mL single-dose vial and 5-mL multidose vials; 80 mg/ mL (as sodium succinate) in 1-mL single-dose vial. Given i.v. daily	
Dexamethasone	1 mg = 25 mg hydrocortisone Injection: 4 mg/ mL in 1-mL ampoule (as disodium phosphate salt)—i.v. in 4 doses/day Oral liquid: 2 mg/5 mL Tablet: 2 mg [EMLc]; 4 mg	0.5 mg/m^2 Daily (early morning)[a]
B. Management of TSH-thyroid hormone deficiency		
Levothyroxine	Tables: 25 µg, 50 µg, 100 µg	
	Start with 50 µg/m^2 daily, oral Increase by 25 µg as needed until free T4 is near the upper limit of the normal range (minimum testing interval is 7 days) The dose can be rounded up/down to multiples of 12.5 or 25 if tablets are scored The dose can be alternated daily to achieve an average of the desired dose, e.g., 50/75	
C. Management of ADH hormone deficiency (diabetes insipidus) *Be aware that children with hypothalamic involvement preoperatively and/or postoperatively may be unaware of thirst and so do not self-correct dehydration resulting from inappropriate polyuria, sweating, or other fluid losses. They may appear un-distressed with very high serum sodium. These children need meticulous attention to intake and output and frequent weighing, with DDAVP and fluid intake adjustments according to clinical assessment of hydration, fluid balance, serum, and urine osmolality if available, or urine specific gravity in lieu of osmolality.*		
Desmopressin (DDAVP)	Injection: 4 µg/mL in 1 mL ampule: Given s.c., i.m., or i.v.—0.025 µg/kg (max 4 µg) in 1-2 doses/day	
	Nasal spray: 10 µg/spray (100 µg/mL): Although difficult to access from the dispenser, the solution can be used as 1 µg = 1 unit of insulin syringe added to a small volume of normal saline for nasal administration 1 month-2 years: 1-5 µg 12 hourly 2-12 yestabuars: 5 µg 12 hourly > 12 years: 5-10µg 12 hourly	
(not on WHO EML)	Tablets: 100 µg/200 µg (0.1 mg/0.2 mg) 1 month-2 years: 10 µg 2-3 × daily 2-12 years: 50 µg 2-3 × daily > 12 years: 50-100 µg 2-3 × daily	
Start with lowest dose and titrate by symptoms in older children, and serum sodium and osmolality in young children unable to drink independently		

(Continued)

TABLE 4 (Continued)

D. Management of LH/FSH-sex steroid deficiency	
Estrogen	• Oral contraceptives: 30-35 μg of ethinylestradiol • Injectable contraceptives: 5-mg estradiol cypionate Estrogens listed but not specified Induction of puberty: start with the smallest dose of estrogen possible (starting dose ethinyl estradiol 2 μg, and estradiol 5 μg *neither on WHO EML*) and increase six monthly to full replacement over two years. Start cycle at 18 months-2 years or if vaginal bleeding starts before then. Cycling can be achieved with menopausal hormone replacement therapy, low-dose oral contraceptive, or oral progestogen for 10 days of the cycle. See resources for alternatives if resources permit.
Testosterone	• Testosterone injection: 200 mg (enanthate) in 1 mL ampule Induction of puberty: Start at 80 mg/m^2 intramuscular injection every 4 weeks. Increase by 50 mg every 6 months until standard adult dose is reached: 250 mg i.m. every 4 weeks—200 mg i.m. every 2 weeks. Note that the testes will remain small
Discuss secondary sexual characteristics and health benefit of sex steroid replacement vs fertility.	
E. Management of growth hormone deficiency	
Somatropin *(not on WHO EML)*	• 25-35 μg/kg/day, subcutaneous injection—(not on EML) About 30% of children have "growth without growth hormone"—the cost-benefit of giving these children growth hormone is unclear (weight benefit not established, adult QoL). If resources permit, consider a trial of GH replacement to establish benefit in an individual child.

Abbreviations: ADH, antidiuretic hormone; EMLc, essential medicines list for children FSH, follicle stimulating hormone; GH, growth hormone; i.m., intramuscular; i.v., intravenous; LH, luteinizing hormone, μg, microgram; mg, milligram; QoL, quality of life; SAMF, South African medicines formulary; s.c., subcutaneous; TSH, thyroid stimulating hormone; WHO EML, World Health Organization Essential Medicines List.
[a]SAMF: South African Medicines Formulary 12th edition 2016.

Postoperative care should ideally be managed in PICU or in a ward with experienced nurses to manage patients with electrolyte imbalance. Children are prone to different complications in the perioperative and postoperative period; DI, which can be transient or permanent, partial or complete, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and cerebral salt wasting, all of which can be challenging to manage.[38] DI is the most common; it often runs a triphasic (DI followed by SIADH then DI) or unpredictable course in the early postoperative period; therefore, one should avoid placing patients on regular, repeated doses of DDAVP before the pattern becomes established.

In the immediate postoperative period:

1. Monitor fluid balance meticulously. Use a urinary catheter for an accurate measurement of urine output.
2. Use normal (0.9%) saline intravenously at 2/3 of maintenance requirement.
3. Replace excess urine output with water via nasogastric tube or half-normal (0.45%) saline intravenously.
4. Replace any additional excess loss (stool, CSF, drains) with normal (0.9%) saline six hourly.
5. Monitor urea, electrolytes, and osmolality (measure or calculate*) immediately and eight hourly. Increase monitoring to four to six hourly if serum sodium (Na) increases by ≥5 mmol/L.
6. Continue corticosteroid stress doses for 48 hours.

*Calculated osmolality = 2×Na + 2×K + glucose + urea (all in mmol/L) or $2\times Na + 2\times K + \frac{Glucose}{18} + \frac{urea}{2.8}$ if glucose and urea are in mg/dL.

5.2 | Radiotherapy

Preoperative MDT assessment will assist in overall patient management. Specifically, deciding whether near total resection (NTR)/GTR, conservative surgery with postoperative radiotherapy, or cyst decompression/CSF diversion alone should be attempted is key.[51] Factors such as tumor size (> 2-4 cm), preoperative hypothalamic involvement, hydrocephalus at presentation, and younger age are deemed high risk for surgical morbidity and may favor conservative resection and postoperative radiotherapy.[8]

The timing of the radiotherapy has been studied, with some suggesting that radiotherapy can be deferred in some cases, especially in younger children, because of the risk of late effects. However, deferring radiotherapy may be associated with worse outcomes.[15,52-54] Therefore, the risks of deferring radiotherapy have to be balanced: i.e., the increased morbidity relating to multiple recurrences and multiple surgeries.[55] Even in cases of NTR, recurrence rates are still high, and earlier radiotherapy may improve outcome.[56] If it is elected to omit adjuvant radiotherapy, it can be offered at the time of recurrence either alone or in combination with surgery. A smaller tumor and a child with an intact hypothalamic-pituitary axis, especially if preadolescent, would add weight to the argument for delayed radiotherapy.

5.2.1 | Technique

When radiotherapy is proposed, a suggested guideline for LMIC is presented in Table 5.

Many differing modalities have been used, including intracystic radioisotope treatment, gamma knife, or linear accelerators (LINAC)–based radiosurgery, fractionated radiosurgery, and proton beam therapy. However, as more LMIC centers are expected to be equipped with conventional external beam technologies, guidelines will focus on this modality. Conformal radiotherapy (3D-CRT), as opposed to 2D techniques, has a more precise coverage of the tumor with reduction of the margin and volume of normal tissue irradiated leading to lesser toxicities.

Acute radiotherapy side effects are rare and mainly related to radiation-induced cyst expansion. Late radiotherapy side effects may include cognitive decline, hypothalamic-pituitary dysfunction, visual deterioration, and less commonly, vasculopathy or necrosis and secondary tumors.

5.2.2 | External BEAM radiotherapy treatment

2D RT guidelines in LMIC

We do not recommend using 2D radiotherapy unless access to 3D-CRT is unavailable. In such cases, the use of at least three beams and beam shaping is suggested (so-called 2.5D radiotherapy).

A thermoplastic cast is used for immobilization. Patients are imaged in the supine position, with flexed head position. The position of the tumor is localized on lateral and frontal simulator films, using the diagnostic CT images for obtaining tumor dimensions and the position of the tumor relative to bony skull structures. Three beams are placed (right and left lateral, and anterior). The axis (plane) of treatment is drawn onto the cast during simulation, taking care to ensure that the chin is adequately flexed so as the anterior beam enters above the eyes. The patient's contours and proposed fields are transposed onto paper in all three views (axial, midline [sagittal], and coronal), and manual planning is used.

When 2D radiotherapy is unavoidable, two lateral parallel opposed beams are used. With the target position measured from the CT, ensuring the exact position of the lateral radiotherapy fields on a simulator lateral skull field is challenging, and the following measurements are required: distance from superior skull to superior aspect of tumor, anterior skull to anterior aspect of tumor, and posterior skull to posterior aspect of tumor. The tumor position inferiorly, in relation to the pituitary, is also noted. Block edges will be placed at a minimum of 2 cm from the tumor for cobalt radiotherapy and 1 cm for 6× LINAC radiotherapy beams (Supporting Information Figure S4).

3D-CRT guidelines in LMIC

3D-CRT has the advantage of utilizing CT imaging to provide precise coverage of the tumor with reduction of the radiotherapy field margin, beam shaping, and consequently a reduction in the volume of normal tissue inevitably irradiated, leading to lesser toxicities.[55]

Immobilization, positioning, and imaging

A thermoplastic cast is used for immobilization. Patients are scanned in the supine position, with a neutral to slightly flexed head position. The CT scan is performed using 3 mm slices, in order to obtain high-quality digitally reconstructed radiographs during treatment verification.

Defining the target volumes

Although CT is required for calculating the dose of radiation via the treatment planning system, MRI (when available) is useful in assisting with target volume delineation, and most modern planning systems have the capability to register (fuse) the MRI with the planning CT. The use of intravenous contrast for the planning CT aids in target delineation when MRI is not available. Preoperative scans should be available to help inform tumor volumes.

Gross tumor volume (GTV) is defined as any residual tumor and/or the tumor bed (not including the surgical path).[57] All cystic areas should be included in the GTV. Clinical tumor volume (CTV) margin should encompass any areas of uncertainty, especially along the skull base. Any areas of invasion or attachment presurgery should be identified carefully and included in the CTV. When the tumor occurs at a geographical boundary, e.g., at the bony and meningeal interfaces, the CTV margin is zero (0 mm), while at brainstem interfaces or in areas of uncertainty, the CTV margin may be 5-10 mm.[58]

The planning tumor volume (PTV) is a geometrical margin expansion surrounding the CTV. This margin depends on the reliability of the set-up, immobilization, delivery methods, and verification frequency in individual departments. The PTV margin is usually in the order of 5-10 mm for intracranial radiotherapy. Reduction of margins is possible only when a stringent quality assurance and portal imaging protocol is applied. Organs at risk to be contoured include eyes, lenses, optic nerves, chiasm, temporal lobes (or hippocampi), brainstem, cochleas (Supporting Information Figure S5). Several online contouring guides for delineation of normal structures are available.[59] Normal tissue dose constraints should be guided by QUANTEC/PENTEC.[60-64] A general guide to the treatment of children in LMIC with radiotherapy is available.[65]

Planning techniques

Midline suprasellar tumors are usually treated with a minimum of three beams. Eccentrically located tumors may differ. However, standard beam arrangement would include a right and left lateral beam and an anterior beam. The lateral beams may be angled slightly posteriorly in order to better protect the cochleas, and the anterior beam may be noncoplanar in order to better protect the eyes. In this case, the couch is placed in a 270-degree position and the vertex (anterior beam) is angled to enter above the eyes. Typically, the anterior beam is weighted slightly higher than the two lateral beams, as the frontal lobe tends to be slightly more resilient to late effects than the temporal lobes. A total dose of 50-55 Gy is used in daily doses of 1.8 Gy in order to limit late toxicity.

Treatment verification

Dosimetric verification is institution specific. Geometric verification depends on the equipment available and time constraints. In LMIC,

we suggest a minimum of positional verification using portal imaging/electronic portal imaging device/cone-beam CT (CBCT) on days 1-3, to exclude systematic errors and weekly thereafter.

Ideally, cyst size should be monitored during a fractionated course, as approximately 20%-30% of cysts will have a transient increase in size and some patients will require replanning (Table 5). Monitoring can be done by scheduling a limited CT halfway through treatment, and comparing this to the planning scan, by use of contrast in the Ommaya reservoir (if the patient has one) and a comparison of the cyst to the planning scan or by more sophisticated methods such as CBCT if available. Monitoring postradiotherapy may be required for transient cyst enlargement.[66]

5.2.3 | Volumetric modulated arc therapy (VMAT) radiotherapy

In recent years, newer low-energy linear accelerators, with VMAT capability, have become available. In particular, machines requiring less electrical usage, and less staff input, have made VMAT-capable LINACs a possibility as replacement for cobalt machines in LMIC. Instituting VMAT techniques, however, must be accompanied by a stringent quality assurance program to ensure accuracy, but may be beneficial when treating children with brain tumors as highly conformal target doses and limiting dose to critical structures is possible (Supporting Information Figure S6).

5.2.4 | Stereotactic radiosurgery

This is reserved for very small tumors (volume < 3.5 mL) or for tumors more than 3 mm away from the optic chiasm. Tumors larger than 3.5 mL treated to doses of more than 11.5 Gy marginal dose have a relatively high risk of opticoendocrine complications (> 15%).[63] However, particularly when a single fraction is used, this technique would impose a significant risk of injury of brain tissue and optic structures and therefore is not recommended in children with craniopharyngioma. Fractionated radiation is the treatment of choice in children.

5.3 | Intracystic therapies

Intracystic therapies should be considered to treat predominantly previously untreated cystic tumors, or cystic progression after previous surgeries or radiotherapy, mainly to avoid further surgery or delay radiotherapy particularly in children < 5 years old. Currently, the intracystic agent with the widest use is INF alpha.[17] Interferon alpha-2b (Intron A) and interferon alpha-2a (Roferon A) both can be used as an intracystic therapy in craniopharyngioma as 3.000.000 IU in 1.5 mL preservative free normal saline, and a detailed technical guide on how to use it was previously published.[16,67] When using this technique, tumor volume decreases through two mechanisms: sequential aspiration of the cystic content and increased apoptosis.[18,67]

A cooperative study included 60 patients with solid cystic craniopharyngiomas including 39 (65%) treatment naïve. Overall, 78.3% of the patients obtained at least a 50% reduction in volume with an average of five cycles, and only 13.3% presented new endocrine dysfunction; further, only 30% experienced minor complaints such as palpebral edema, fatigue, fever, and arthritis.[17] Patients need to be selected carefully, preferably when the intracystic component is > 60%, and this technique should only be used if the team is comfortable. The catheter is coupled with an Ommaya or Rickham reservoir (preferably with a lateral exit). Implantation can be with different techniques: by endoscopy when associated with hydrocephalus, by free-hand when the cyst is very large, and by navigation stereotaxis (if available) or by craniotomy.[68] If INF is not available, frequent cyst aspirations may help.[69] The use of intracystic Bleomycin is not recommended due to the potential of significant neurological complications.[70,71]

The main challenges with intracystic therapies in LMIC are the availability of reservoir catheters or INF treatments, drug costs, and neurosurgical expertise. Administration three times/week may be challenging for families living distantly. However, the favorable safety profile makes this treatment a suitable option in cystic tumors to try to delay/avoid radiotherapy and surgery.

5.4 | Treatment of recurrent craniopharyngioma

Although recurrence is a problem in childhood craniopharyngioma, OS is favorable and interventions need to be considered carefully in order to preserve visual, endocrinological, and neurocognitive/psychological functions. Consideration by an appropriately staffed MDT is essential not only at the time of initial diagnosis but at any time of progression or recurrence to consider the risks and benefits of surgery (Table 6).

Initial interventions and subsequent treatment decisions as well as patient's age and location of relapse will determine treatment options at the time of recurrence. In general terms, surgical intervention(s) will be necessary whenever there are signs of increased intracranial pressure or acute visual deterioration. Each surgical intervention should be mindful of further morbidities. In the presence of radiological progression in an asymptomatic child, careful observation is a reasonable option.

In the absence of successful prospective randomized trials, there are no evidence-based data that would allow the outline of a streamlined treatment guideline but there is international consensus to an MDT approach where possible and the lifelong need for careful ophthalmological, endocrinological, and neurocognitive/psychosocial follow-up in children with craniopharyngioma. In LMIC, the ability to treat and manage any consequences of treatment must be carefully assessed before embarking on any particular treatment pathway.

TABLE 5 Radiotherapy guidelines for craniopharyngioma

Service level	Level 0	Level 1	Level 2	Level 3	Level 4
Radiotherapy treatment guidelines for cranio-pharyn-gioma	Refer to level 2 or above	2D radiotherapy to be used only when referral to higher center not possible	2.5D or 3D planning with use of > 2 beams for improved conformity. Either cobalt or linac machines are acceptable. Should have capability to deliver at least four fractions per week and do portal imaging for verification. Otherwise refer to level 3.	Image-guided planning with MRI image registration (fusion) is desirable. Highly conformal 3D or VMAT radiotherapy with on-board imaging capability, five fractions per week.	When available, proton radiotherapy is preferred method; otherwise, image-guided highly conformal radiotherapy (VMAT) is acceptable.
Positioning	N/A	Supine. Thermoplastic mask for immobilization. Flexed neck position.	Supine in a head rest, thermoplastic mask for immobilization. Flexed neck position. Anesthesia for assisting immobilization for appropriately selected patients.	Supine in a head rest, thermoplastic mask for immobilization. Anesthesia for assisting immobilization for appropriately selected patients.	Supine in a head rest, thermoplastic mask for immobilization. Anesthesia for assisting immobilization for appropriately selected patients.
Simulation/ planning CT	N/A	Diagnostic CT with scale used to determine position of tumor on lateral skull X-ray. Parallel opposed lateral fields placed with 2 cm margin on tumor.	CT planning image acquisition or CT simulation is recommended for definitive cases. Obtain a treatment planning CT using a ≤3 mm image section thickness if possible. Contrast is not required but desirable if MRI is not available.	CT planning image acquisition or CT simulation is recommended for definitive cases. Obtain a treatment planning CT using a ≤3 mm image section thickness. Contrast is not required if MRI image registration available.	CT- and MRI-based simulation defined by institutional protocol
Treatment planning	N/A	A central dose (mid-plane dose) prescription is used.	Prioritize these patients for 3D conformal planning. If full 3D conformal planning is not available, using three field techniques (two lateral and an anterior vertex-beam through forehead above eyes is used)	3D conformal planning using noncoplanar beams OR VMAT planning. MRI image registration is desirable. Both preoperative and postoperative imaging should be imported. For postop imaging, T2 sequence and T1 sequence with contrast should be imported and coregistered with planning CT.	Institutional protocols for VMAT or proton planning
Target volumes	N/A	N/A[a]	GTV is defined as residual gross tumor as visualized on planning CT. GTV is expanded by 5-10 mm to create CTV. CTV should then be expanded to take into account preoperative imaging so that all areas of original tumor bed are included. CTV can be edited to exclude tissue with geographical boundary not invaded by tumor. CTV is expanded geometrically for set-up uncertainty to create the PTV. (Expansion is usually 3-5 mm when daily portal imaging is done or 5-10 mm if weekly portal imaging) When 2.5D is used, then CT imaging is used to measure tumor which is drawn manually onto right and left lateral and anterior field views. GTV is then expanded by at least 2-3 cm if using cobalt beams.	Preoperative GTV is drawn on preoperative images using preoperative MRI with coregistration with planning CT. Postop GTV is drawn using postop MRI and CT to identify residual tumor. CTV is then drawn to incorporate residual tumor plus a margin of 5 mm, which is then expanded to include tumor bed using preop GTV as a reference. CTV is edited at geographical boundaries. CTV is expanded by a geometrical margin to account for set-up uncertainty creating PTV (usually 3-5 mm)	Conformal photon target volumes are similar to what is described for level 3, proton guidelines as per institutional protocols

(Continues)

TABLE 5 (Continued)

Service level	Level 0	Level 1	Level 2	Level 3	Level 4
Target doses (definitive)	N/A	A total dose of 50-54 Gy at 1.8 Gy per fraction delivered five fractions per week.	A total dose of 50-54 Gy at 1.8 Gy per fraction delivered five fractions per week.	A total dose of 50-54 Gy at 1.8 Gy per fraction delivered five fractions per week.	A total dose of 50-54 Gy (or 50-54 Gy cobalt Gray equivalent) at 1.8 Gy per fraction delivered five fractions per week.
Treatment techniques	N/A	Parallel opposed beams.	3D conformal treatment using noncoplanar beams where possible to spare normal tissue. If coplanar beams only are available, then maximum chin flexion allows for the anterior/superior third beam to be treated using coplanar beams.	3D conformal treatment using noncoplanar beams where possible to spare normal tissue.	Not for discussion in this context
Treatment delivery and quality assurance	N/A	Portal imaging on day one.	Verification portal imaging should be done on days 1-3 to determine whether any systematic error exists, and a shift is applied where necessary to account for this. Minimum weekly portal imaging for quality assurance. Dosimetric verification should be done before the third fraction.	Verification portal imaging should be done on days 1-3 to determine whether any systematic error exists, and a shift is applied where necessary to account for this. Minimum weekly portal imaging for quality assurance. Where possible, daily kV on-board imaging or cone-beam CT may be considered to reduce set-up margins (based on institutional protocol). Note: A 3-mm PTV margin expansion requires daily image guidance and intervention prior to treatment. A 5 mm PTV margin expansion has no special requirements. Dosimetric verification should be done before the third fraction.	Not for discussion in this context
Special considerations	N/A	N/A[a]	Note that cystic craniopharyngioma may expand during radiotherapy. A limited CT (or T2 weighted MRI) done halfway is therefore desirable in order to check that treatment volumes are still adequate.	Weekly CBCT or weekly limited T2 weighted MRI during radiotherapy is desirable to determine whether any cyst expansion has occurred. Adaptive volumes and plan should be implemented as necessary.	

Abbreviations: CBCT; cone-beam computed tomography; CT, computed tomography; CTV, clinical tumor volume; GTR, gross tumor volume; MRI, magnetic resonance imaging; N/A, not available; PTV, planning tumor volume; VMAT, volumetric arc therapy.
[a]N/A: please see the text for details on special circumstances

6 | SEQUELAE AFTER CRANIOPHARYNGIOMA

Major sequelae after childhood-onset craniopharyngioma include disease- and/or treatment-related visual, neurologic, neuroendocrine, and neuropsychological deficits.[72] Follow-up care, provided by an experienced MDT, should focus on clinical and MRI monitoring for recurrences/progression, endocrine replacement, prevention and therapy of long-term side effects, and improving QoL after craniopharyngioma.[73]

Metabolic syndrome resulting from hypothalamic damage occurs in approximately 50% of craniopharyngioma survivors[2,74,75] and is associated with increased cardiovascular risk,[74] abdominal fat

TABLE 6 Ideal follow-up of children diagnosed with craniopharyngioma

	Time points	Procedures	Parameters	Evaluation	Interventions
Clinical assessment	Baseline assessment after surgery, further on at six months intervals. Intervals should be increased or decreased based on the patient's individual situation.	History, physical and neurological status	Edema, daily fluid intake and urine output, eating behavior, physical activity	Obesity, water-sodium-balance, neurologic deficits	Modification of desmopressin medication, teaching on flexible and appropriate dosage
Anthropometry	Six months intervals during first year postsurgery, further on yearly intervals.	Height, weight, waist circumference	Height, weight, waist circumference, pubertal stage	Growth velocity, BMI, waist-to-height ratio, Tanner stages	GH substitution, increasing physical activity, diet, puberty induction/suppression
Imaging	Three months after surgery, Six months intervals during first three years postsurgery. [a] Intervals should be increased based on the patient's individual imaging.	MRI: T_1-weighted sagittal and coronary images (max. 3-4 mm thick slices) and proton- and T2-weighted axial images of the entire brain	Ventricle size, tumor size, growth toward optic chiasm and hypothalamus, cystic compartments, calcifications	Progression of cystic and/or solid parts, hydrocephalus, pressure on optic chiasm, hypothalamic involvement	In case of progression, multidisciplinary decision on surgery, cyst drainage, cystic interferon alpha instillation, irradiation
Ophthalmology	Baseline assessment after surgery, further on at six months intervals. Intervals should be increased or decreased based on the patient's individual situation.	acuity, fundus, visual field, when appr: color vision, oculomotor function	Visual acuity, Goldman perimetry	Deterioration of visual status might indicate tumor progression or sequelae	In case of deterioration: MRI
Endocrinology	Baseline assessment after surgery, further on at six months intervals. Intervals should be increased or decreased based on the patient's individual situation. Patients with uncomplicated course of disease may not need frequent follow-up.		fT4, IGF-I, morning cortisol (if not on replacement), serum sodium If obese: HbA1c, lipids, ALT, Cr, uAlb/Cr, basal gonadotrophins in absence of secondary sexual characteristics in girls > 13 years and boys > 14 years	Appropriate evaluation and substitution of endocrine deficiencies	Teaching on flexible and appropriate dosage of endocrine substitution and awareness/ emergency procedures in case of imminent addisonian crises.
Bone age	Yearly intervals	X-ray left wrist	Bone age/skeletal maturity	Greulich and Pyle or available standard	Assessment of pubertal development, final height prognosis
Sleep pattern/ school perfor-mance/ behavi-oral changes	Yearly intervals. Intervals should be increased/de-creased based on the patient's individual situation.	History	Daytime sleepiness, day fatigue, depression, aggressive behavior, memory	Psychological assessment, sleep calendar	Melatonin (if available). Psychological interventions.

Abbreviations: ALT, alanine transaminase; BMI, body mass index; Cr, creatinine; fT4, free T4; GH, growth hormone; HbA1c, hemoglobin A1c; IGF-I, insulin-like growth factor; MRI, magnetic resonance imaging; uAlb/Cr; urine albumin creatinine ratio.

[a]This may not be achievable in some centers, and although the suggestions are ideal, imaging should be performed within the constraints of the available facilities in each unit.

distribution,[76] nonalcoholic fatty liver disease,[77] and impaired QoL.[2] Disturbances of circadian rhythms such as increased daytime sleepiness,[78] fatigue, and eating disorders,[79,80] pulmonary and gastrointestinal complaints (dyspnea, diarrhea),[2] neuroendocrine deficiencies,[2] memory deficits, and neuropsychological deficits (irritability, conduct disorders, depressive symptoms, aggressiveness)[81-85] are major long-term sequelae in craniopharyngioma patients suffering from hypothalamic syndrome. Twenty-year OS is reduced in patients with hypothalamic involvement of childhood-onset craniopharyngioma.[2,86]

7 | FOLLOW-UP CARE AFTER CRANIOPHARYNGIOMA

Regular monitoring by imaging (preferably MRI because of radiation associated with serial CT imaging) for detecting relapse or progression is recommended at increasing postoperative intervals (Table 6). When routine follow-up imaging is not readily available, then a referral for imaging can be based on deteriorating visual symptoms or new neurological deficits. Based on recent reports,[2] endocrine complications such as addisonian crises and fluid imbalances due to DI are risk factors for impaired survival. Accordingly, regular endocrine monitoring and educating patients with craniopharyngioma and their families are recommended.

Pharmaceutical treatment options for hypothalamic obesity with central stimulating agents and other substances such as oxytocin[87-91] have been tested with mixed results.[72]

With regard to neuropsychological deficits, episodic memory recall deficiencies largely sparing other memory components and increased apathy have been reported in survivors with hypothalamic lesions.[81,92,93] Unfortunately, reports on the effectiveness of neuropsychological therapeutic interventions are rare and may not be relevant in LMIC.

Table 6 lists recommended follow-up monitoring. Clinical, neuroradiological endocrine and ophthalmological check-ups should be performed at baseline after diagnosis/surgery and further on at six months intervals. Frequency of monitoring should be increased or decreased based on the patient's individual situation. Patients with uncomplicated course may not need frequent follow-up.

8 | CONCLUSIONS

The management of craniopharyngioma is complex and challenging even in HIC; however, the burden of this tumor may be more overwhelming in LMIC. This is related to not only limited neurosurgical resources or lack of advanced radiotherapy facilities, but also the limited resources to deal with consequences of treatment on cognition, behavior, obesity visual deficits, and endocrinopathies. Craniopharyngioma is a chronic condition, and it is important to consider the treatment option that causes the least harm and limited intervention (e.g., cyst decompression/CSF diversion) may be the right option in certain circumstances as it will delay the potential need for radiotherapy/surgery. For all these reasons, craniopharyngioma ideally needs MDT discussion during every step of management in an attempt to limit and/or manage these consequences. The team needs to consider the availability of resources and the possibility of future follow-up when considering treatment plans.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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ORCID

Nisreen Amayiri https://orcid.org/0000-0002-7972-5885
Hermann L. Muller https://orcid.org/0000-0003-4929-9966
Jeannette Parkes https://orcid.org/0000-0002-7735-1111
Yacoub A. Yousef https://orcid.org/0000-0001-7750-6454
Michael Sullivan https://orcid.org/0000-0002-8606-5889
Marcos Devanir da Costa https://orcid.org/0000-0003-3552-6347
Alan Davidson https://orcid.org/0000-0002-4646-4332
Eric Bouffet https://orcid.org/0000-0002-6832-6539
Simon Bailey https://orcid.org/0000-0003-4763-4329

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Author/s:
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