NARRATIVE REVIEW

Consensus guidelines for the management of craniopharyngioma in low- and middle-income countries

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Abstract

Craniopharyngiomas are benign, extra-axial epithelial tumours originating from the pituitary stalk, impacting areas such as the hypothalamus, optic chiasm, and various cranial nerves. These tumours present unique surgical challenges due to their proximity to critical neurovascular structures. Management typically involves maximal safe resection as the primary approach. However, in low- and middle-income countries (LMICs), factors like late presentation, higher risks of endocrine and visual complications, frequent recurrence, and potential for incomplete resection complicate treatment. These challenges are exacerbated by limited access to specialised expertise and surgical equipment, increasing the risk of damage during surgery compared to High-Income Countries. This manuscript outlines management guidelines tailored for LMICs, emphasizing that a combination of surgical resection and chemoradiation therapy, as advised by a neuro-oncology tumour board, often yields the best outcomes.

Keywords: Craniopharyngioma, optic chiasm, pituitary gland, hypothalamus, neoplasms, glandular, epithelial

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Introduction

Craniopharyngiomas are extra-axial, benign, epithelial tumours[1] that arise from the pituitary stalk and involve the hypothalamus, pre-chiasmatic cistern, and sub-frontal spaces, third ventricle, foramen magnum, optic chiasm, cranial nerves, sub-temporal spaces, and blood vessels.[2-4] The annual incidence of craniopharyngiomas is around 0.5 to 2 cases per million individuals, which represent 1.2-4% of all paediatric intracranial tumours and 13% of all sellar tumours.[5-7] A bimodal age distribution has been reported, with peaks occurring in childhood (5 to 14 years) and adulthood (50 to 75 years). These tumours are more common in Japan and Africa, but no gender predilection has been reported.[8-11]

In low- and middle-income countries (LMICs) , the lack of resources and socio-economic imbalance serve as limitations for the management of craniopharyngioma, especially when the tumour can have long term implications on the quality of life of patients.[12-14] Treatment outcomes are also significantly inferior in LMICs as compared to high-income countries.[15] Delayed diagnosis can make the management challenging and complex.[16] Our aim is to formulate guidelines for appropriate diagnosis and management strategies for LMICs such as Pakistan.

Methodology

The literature search for high-quality data on craniopharyngioma was done in March 2023, on different databases, including PubMed, Google Scholar, Scopus, and Embase. The most relevant and high-quality studies were analysed to develop evidence-based recommendations. An expert panel was convened consisting of specialists and leading experts within the field of neuro-oncology to identify the gaps in the diagnosis and management of craniopharyngioma within Pakistan. This group was tasked with identifying best-practice recommendations and their application within the context of Pakistan as an LMIC. Recommendations were collated, reviewed, and debated regarding utility and evidence-based practices in a process that has been previously detailed.[17]

Clinical presentation

Craniopharyngiomas usually present with non-specific symptoms such as headache and nausea; however, when the tumour has grown to a size of at least 3 cm, significant symptoms start appearing. These include visual disturbances, endocrine abnormalities, and growth

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hormone deficiency.[6, 18] Endocrine abnormalities may include hypothyroidism (characterised by obesity, constipation, lethargy, and cold intolerance), diabetes insipidus (affecting approximately 15% of the patients, with symptoms such as polyuria and polydipsia, indicating the involvement of the infundibulum of the pituitary stalk),[5,14, 19-21] adrenal failure (orthostatic hypotension, hypoglycaemia, hyperkalaemia, cardiac arrhythmias, lethargy, confusion, anorexia, nausea, and vomiting) [1,19] and other issues such as decreased growth rate, obesity, sexual retardation (manifested as decreased libido, impotence, amenorrhoea), and behavioural changes (hyperphagia and emotional immaturity). Headache and visual disturbances occur due to the mass effect of the tumour, secondary to obstructive hydrocephalus, contributing to increased intracranial pressure and damage to the optic chiasm, respectively. Lastly, elderly patients also present with a cognitive decline and somnolence.[1, 5, 10]

After a thorough clinical history, a general and neurological examination should be performed. In the neurological examination, signs suggesting increased intracranial pressure can be identified.[22] Assessment of the visual acuity (using Snellen's chart and Teller grating cards), visual field, colour vision (using the Ishihara test), and fundoscopy to rule out atrophy and oedema is essential.[23] It is recommended to use growth charts specifically in children, to monitor weight, height, body mass index to monitor for growth rate, use of Tanner staging to assess the development of secondary sexual characteristics,[24] and an evaluation for signs of other hormonal abnormalities, such as oedema, anaemia, altered mental function, orthostatic hypotension, etc.[25]

Initial workup

Neuro radiology

Craniopharyngiomas have a heterogeneously enhancing radiological appearance. They most commonly manifest as suprasellar lesions with diverse development patterns and with intrasellar extension. Childhood craniopharyngiomas show intra-tumoural calcifications and a solid and cystic component.[26-30] A lack of calcification can be confusing; hypothalamic low-grade glioma and suprasellar germ cell tumours are the main radiological differential diagnosis. In this case, a biopsy or resection is necessary for a diagnosis.[14]

Only 20% of the tumours are entirely suprasellar, with predominantly intrasellar lesions are present in less than 5%.29 They typically surround neurovascular systems in the interpeduncular and suprasellar cisterns and may present as totally solid lesions or have an accompanying cystic component. In adults, they often develop posterior to the chiasm in adults and extend back into the third ventricle.[27]

Adamantinomatous craniopharyngiomas typically appear as cystic lesions with or without a solid component on a computerised tomography (CT) scan. With discernible calcifications, they display a nodular enhancement in solid lesions and a rim-like enhancement in cystic lesions. In comparison to the surrounding brain, the mixed tumours appear hypodense on a CT scan. However, because of the high protein concentration, the fluid inside the cysts appears hyper-dense. CT scans are also useful to determine the degree of skull base involvement such as erosion of the sella turcica. Papillary craniopharyngiomas usually appear as solid, are infrequently calcified, and display homogenous contrast enhancement with a thickened pituitary stalk. They infrequently occur as purely intrasellar lesions and are often suprasellar or within the third ventricle.[27, 30]

On T2-weighted images of magnetic resonance imaging (MRI), cysts appear as hyperintense lesions due to their high protein content, whilst the solid components are nodular. The solid lesions appear as iso- and hypo-intense on T1-weighted images and show a variable appearance on T2.

On contrast MRI, the solid part of a craniopharyngioma and the cyst wall typically show more significant enhancement than a pituitary adenoma or the normal gland. To assess the relationship between the tumour and the critical vascular structures, magnetic resonance angiography (MRA) can be useful. Specific elevated peaks of lactate and lipids on magnetic resonance spectroscopy (MRS) differentiate them from the gliomas and pituitary adenomas.[14, 28]

Practical applications to assessment and preoperative planning

Evaluation of the tumour's involvement of the hypothalamus in the pre-operative MRI is essential. It aids in predicting and reducing postoperative hypothalamic morbidity and serves as a key determinant of the extent of resection as pre-operative hypothalamic involvement is recognized as a poor prognostic factor. For diagnostic and surgical planning, both MRI (T1/T2/flair sequences) and CT scans are ideal. T2 weighted MRI sequences are helpful for determining how the tumour interacts with adjacent structures, particularly the optic chiasm, mammillary body, and the third ventricle floor. These sequences are also useful to quantify the size of the tumour and the perilesional edema.[27] Diffusion tensor imaging tractography allows for visualization of the

hypothalamo-hypophyseal pathways.[14, 27]

To prepare for an endoscopic approach, a CT scan is useful for delineating the cystic sections of the tumour and skeletal features including bone erosion, hyperostosis, sphenoid sinus pneumatisation, and septations. When there is a strong suspicion of venous or arterial involvement or when selecting the best surgical strategy in cases of potential problems with the cerebral or cranial base vasculature, a CT angiography can be added.

Evaluating visual function is an essential component of the diagnosis, follow-up, and prognosis of craniopharyngiomas is the evaluation of the visual function. It is crucial to carefully assess the papilledoema, optic nerve atrophy, visual field abnormalities, and visual acuity. Optical coherence tomography is an effective approach for assessing visual impairment and predicting vision recovery. The majority of craniopharyngioma patients present with anterior panhypopituitarism. Therefore, a complete endocrinological assessment is required to reach a diagnosis.[27]

Pituitary hormone deficiencies are present in more than 80% of children at the time of diagnosis, and additional deficiencies can develop during or after treatment. Thus, even in the absence of clinical signs, pituitary function should be assessed in all sellar/suprasellar lesions.[27] Assessment should include each hypothalamic-pituitary dependent hormonal axis should be evaluated including serum TSH, ACTH, morning cortisol, free T4, HGH, IGF-1, prolactin, LH, FSH, progesterone, estradiol, and testosterone levels. Evaluation of serum sodium levels, urinary specific gravity and osmolarity is important to rule out diabetes insipidus, which is seen in 10-20% of the patients.[14, 27] Additionally, the evaluation of visual acuity, color vision, visual field, and optic nerve discs is crucial.[14]

Surgical management

The treatment of craniopharyngioma is challenging due to its location and involvement of the surrounding neurovascular structures. In LMICs, challenges such as late presentation, high risk of endocrine and visual complications, high recurrence rate, risk of incomplete resection, limited expertise, and surgical equipment, and the risk of damage to the surrounding structures during surgery are relatively higher than in HICs.[31-33] Surgical complications include diabetes insipidus, hypothalamic obesity, and visual disturbances secondary to damage to the hypothalamic stalk or optic chiasm.[1, 2, 12, 13]

Treatment options include surgery, radiotherapy, and intracystic therapy. The goal of surgery is to achieve safe tumour resection, without causing further harm.[34] Surgical management options for craniopharyngioma include gross total resection (GTR) and subtotal resection (STR) followed by local radiation.35 GTR refers to the maximal removal (95%) of the tumour. STR involves removing the tumour to the extent that it does not cause any iatrogenic complication. STR is often paired with radiotherapy to manage the part of the tumour left behind and avoid recurrences.[36] A review of the literature indicates that when compared with STR alone, GTR had better outcomes in terms of tumour control; however, when STR was combined with radiotherapy, it showed better outcomes as compared to GTR alone.[37] The literature mentions various surgical approaches for craniopharyngiomas. The selection of a surgical approach depends upon the location of the craniopharyngioma and its involvement of surrounding structures. There are two major approaches: open and endoscopic endonasal. Open approaches (craniotomy) include anteromedial, anterolateral, lateral, and intraventricular (transcortical and transcallosal) approaches. The trans-sphenoidal approach refers to the endoscopic endonasal approach (EEA), which has recently emerged in the last few decades as the preferred approach associated with its benefits.[38, 39]

Studies in the literature show various studies that prefer an endoscopic endonasal approach (EEA) over a trans-cranial approach. EEA offers better visualisation without the need to retract the brain or disrupt surrounding structures, giving direct access to the site where the tumour is located. Specifically, the tumours with a residual lesion and ones with retro-sellar interpeduncular extensions have been found to show better outcomes with EEA.[40] Compared to the transcranial approach, the endoscopic endonasal approach has been shown to achieve gross total resection more frequently, reduced recurrences, a lower increase in FLAIR signals postoperatively,[40] improvements in vision[26,41,42] and fewer complications such as cognitive loss, pseudoaneurysm,[26] new endocrinopathies,[42] seizures[41] and asymptomatic meningitis.43 Patients undergoing open TCA needed adjuvant radiation and were associated with poor prognosis with a higher incidence of postoperative ischaemia, weight gain,[26,] and longer length of hospitalization than EEA.[44] The extent of resection is also comparable in both approaches.[42] Additionally, EEA with a 3-dimensional view allows for better hand-eye coordination and perception of depth. Robotic-assisted EEA is the current area of practice that is being tested in different settings to compare its outcomes with other strategies.[45] However, it has also been noted that the endoscopic endonasal approach should be

avoided in lesions that grow into the middle cranial fossa just adjacent to the internal carotid artery,[40] and EEA results in increased and more frequent CSF leakage than TCA,[41] which requires further management.[38]

Lastly, for the management of hydrocephalus and increased intracranial pressure, surgical debulking or intracystic therapy is usually sufficient; however, in some cases, a pre-operative ventriculoperitoneal shunt, external ventricular drain or endoscopic septostomy may help delay surgery in paediatric populations.[46]

Several factors influence the decision to develop a strategy for the management of craniopharyngioma. In LMICs, the availability of expertise and resources such as surgical instruments, imaging modalities, intensive care units, radiotherapy facilities, intracystic treatment options, and support systems for the long-term management of the disease contributes to the challenge of treating a patient effectively. Therefore, a multidisciplinary approach needs to be considered for deciding management.[16, 47]

Pathological assessment

Histopathology

The World Health Organization (WHO) classifies craniopharyngiomas into two distinct etiologies, Adamantinomatous craniopharyngioma and Papillary craniopharyngiomas. They are mostly found in the suprasellar region, attached to the underlying tissue.[28] Adamantinomatous craniopharyngiomas are usually solid, multilobulated nodules with trabeculae of squamous epithelium bordered by columnar epithelium and abundant calcifications. On histological examination, three components are classically present: keratinizing epithelial cells often with lining of nuclei along the periphery (referred to as 'palisading' appearance), a middle layer made up of loose stellate cells, and fully keratinized epithelial cells with homogenous eosinophilic cytoplasm and degenerated/ empty nuclei (referred to as 'ghost' cells). These cells aggregate into circular bodies called 'wet' keratin (to distinguish from the 'dry' flaky keratin present in dermoid/ epidermoid cysts. Calcification of keratin is often seen. The presence of desquamated epithelial cells and cholesterol in the cyst fluid gives it a distinctive 'motor oil' appearance. Additionally, adamantinomatous craniopharyngiomas tend to adhere strongly to the surrounding tissues, which complicates complete surgical excision.[28,30] Histologically, the surrounding brain can show extensive gliosis with the formation of Rosenthal fibers, often making it indistinguishable from Pilocytic astrocytoma.

On the other hand, papillary craniopharyngiomas resemble the metaplastic respiratory epithelium with a pseudopapillary structure of the epithelial cells. They are lined by ciliated squamous epithelium and goblet cells lacking surface maturation. Unlike adamantinomatous craniopharyngiomas, they arise due to the somatic mutation and lack ghost cells, and 'wet' keratin nodules.[14, 26] The most common biopsy techniques historically have been skull-base or image-guided needle biopsy; more recently, endoscopic transnasal biopsy has gained popularity.[30]

Molecular pathology

CTNNB1 mutations are characteristic of adamantinomatous craniopharyngiomas. The beta-catenin gene coding for CTNNB1 is an adherent junctional protein and is important for the signaling of the WNT pathway. The WNT pathway recognized to control cell division, play a role in tissue formation, and embryology. Disruption leads to uncontrolled proliferation and there is associated with many neoplastic diseases. The mutated CTNNB1 protein is not phosphorylated and hence accumulates in the nucleus promoting the cell proliferation. B-catenin immunohistochemical stain can be used to test for nuclear localisation and can be used to differentiate craniopharyngiomas from other sellar tumours.

Papillary craniopharyngiomas are less invasive, have high recurrence rate and are characterised by BRAF and V600E mutations, which cause activation of the mitogen-activated protein kinase (MAPK) pathway and uncontrolled proliferation of the cells.[28]

Adjuvant treatment

Radiation therapy

Radiotherapy can control localised craniopharyngiomas after sub-total resection with an 80–85% success rate.48 Recently a hypothalamus-sparing surgical approach followed by localised conventionally fractionated radiotherapy has become popular due to the significant complications following radical treatment. Radical excision should not be performed for larger adherent lesions evaluated in accordance with developing criteria; Radiation therapy after partial resection may slow down tumour growth without causing hypothalamic dysfunction.[49, 50] Recurrent, residual, and partially excised tumours are treated with radiotherapy. A 90% 10-year progression-free survival rate is seen with radiotherapy.[50]

Factors favouring postoperative localized radiotherapy include larger tumour size at presentation (which is > 2-4 cm) preoperative hypothalamic involvement, hydrocephalus, and younger age of the patient, since

complete surgical excision is not always attainable in these circumstances.[14, 51, 52] Adjuvant radiotherapy is not recommended for individuals with complete excision unless tumour regrowth occurs during follow-up and in children less than 5 years of age.[14,48, 53]

Postoperative radiotherapy can have some adverse effects later in life.[48] Neurocognitive and neuropsychological impairment, visual deficiencies, endocrinopathies, eating issues, and sleep difficulties are some of the side effects of radiation. Due to pre-existing endocrine deficiencies at the time of diagnosis or after surgery, it is challenging to estimate the precise incidence of post-radiation endocrinopathies from the literature. The most likely affected hormone is growth hormone, while thyroxine is the most radio-resistant.[53] The idea that the hypothalamus is more radiosensitive to the effects of radiation than nearby pituitary tissue is supported by literature, which shows that a radiation dose of [27] Gray (Gy) to any volume of the hypothalamus increased the chance of endocrinopathy by a factor of four.[28, 54] Relatively few patients experience DI and hypopituitarism after restricted surgery and radiotherapy.[48]

Highly conformal radiation treatment planning and delivery using intensity modulated radiation technique IMRT or volumetric modulated arc therapy (VMAT) capable linear accelerators have replaced cobalt machines.[14] Recent advancements in radiation therapy techniques, like stereotactic radiation therapy for precise immobilisation and proton beam radiation therapy, may be able to lower the radiation dose to healthy brain tissue further while still providing effective local control.[26] A Multidisciplinary approach involving all stakeholders, including paediatric neurosurgeons and medical and radiation oncologists, is required for maximum clinical outcomes, and peer review is an essential step or component of this critical process.

A total dose of at least 54 Gy in 30 fractions of 1.8 Gy per fraction is recommended. Treatment shall be delivered with daily image guidance, five days a week, once daily. There is evidence suggesting better control with dose escalation.[27,28] Hypofractionated treatment like stereotactic radiosurgery (SRS) is not recommended there is a special situation of very small size residual disease.

Intracystic/systemic therapy

Cystic tumours that have gone untreated or that have progressed following prior treatment can benefit from intracystic therapy, especially in children under the age of five.[14] After maintaining the integrity of the cyst wall, intracystic interferon-alpha may also be a therapy option for primary cystic lesions to prevent the need for alternative therapies depending upon the availability.[26] With an Ommaya or Rickham catheter, intracavitary agents can be instilled to treat cystic recurrences. The use of intracystic Bleomycin is not recommended due to the potential of significant neurological complications.[14] The most widely used agent is INF alpha.

Although systemic therapy is typically not used, a limited series has demonstrated that using subcutaneous peginterferon alpha-2b to treat cystic recurrences can produce long-lasting results.[14] The availability of reservoir catheters or INF treatments, pharmacological pricing, and neurosurgeon experience are the main obstacles to intracystic therapy in LMIC.[14]

Post-operative management and follow-up

Post-operative care for craniopharyngioma can be quite intensive as the risk of developing diabetes insipidus, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and cerebral salt wasting is very high. Constant monitoring of the patient for fluid balance, electrolyte and urea levels, and serum osmolality, preferably in PICU/ICU, is recommended. Postoperative antibiotic administration should include a fourth-generation cephalosporin, vancomycin, or trimethoprim-sulfamethoxazole for the first 24 to 48 hours post-surgery.40 Long-term regular follow-up in clinics for examination for visual and neurologic deficits and endocrine abnormalities is recommended.[55]

Prognosis/quality of life/recurrence

The rate of recurrence is 20–27%. Ten-year progression-free survival has been reported at 84–100% when patients undergo limited surgical resection followed by radiotherapy.[11] Management for recurrent craniopharyngiomas is more challenging and depends upon the patient's age at the time of recurrence and the extent of the tumour.[37] However, in patients who show progression of the disease only on imaging without clinical manifestations, careful observation on a regular basis is suggested. A repeat surgery increases the risk of morbidity and mortality secondary to the disruption of normal anatomical planes from previous surgery due to scarring making dissection more difficult, compounded with recurrent tumours being more closely attached to important neurovascular structures.[41, 56]

Some sources suggest that patients with craniopharyngioma should be offered a surgical treatment in recurrent presentation, and radiation therapy should be offered only when the second surgery fails to produce favourable outcomes.[41] There is conflicting evidence for a favourable approach for treating recurrent craniopharyngioma. While some

Table-1: Summary of Recommendations for Craniopharyngioma.

Initial Evaluation	**Radiology** • MRI brain with and without contrast. • 'Minimum required' MRI brain protocol: o Imaging on at least 0.5T o Sequences: Axial and coronal T2 and coronal or axial FLAIR sequence; pre-contrast T1 and contrast-enhanced T1. • CTA/MRA is recommended if there is significant lateral and posterior extension and involvement of major vessels. • Tumour size, location, margins, enhancement pattern, presence of mineralisation, relation with the chiasm, hypothalamus, pituitary gland and stalk, and third ventricle. • Postoperative MRI is recommended after 3 months. o To identify the extent of resection. o To have a baseline to compare successive imaging. o Not required after biopsy. **Endocrine evaluation** **Ophthalmology assessment** • Visual acuity, perimetry, OCT, and fundoscopy are recommended.
Neurosurgery	• Surgical goals: Maximal safe resection of tumour. • Ommaya insertion with or without biopsy is advised in cystic lesion with high surgical risk. • Small asymptomatic lesions can be followed with serial MRI. • Redo surgery can be considered in case of recurrence/disease progression after risk stratification in NOTB.
Neuropathology	• Haematoxylin and eosin (H&E) preparation for histological typing.
Medical and Radiation Oncology	• Follow regional NOTB recommendations for chemotherapy. • Radiation therapy is recommended after STR for residual disease or recurrence after GTR. • Shall be avoided in children less than 10 years old. • Other factors that warrant radiotherapy include preoperative hypothalamic involvement, hydrocephalus, and younger age of the patient since complete surgical excision is not always attainable in these circumstances. • Radiation therapy is delivered 54 Gy over 30 fractions with conventional fractionation using a highly conformal treatment delivery technique. IMRT/VMAT is preferred over 3D-CRT.

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Follow-up	• First follow-up at post-op day 10 for wound assessment, stitch removal, discussion related to histopathology, and NOTB recommendations. • Clinical follow-up with MRI after 3 months, then 6 monthly with a paediatric oncologist and endocrinologist.

MRI: Magnetic resonance imaging, FLAIR: Fluid-attenuated inversion recovery, CTA: Computed tomography angiography, MRA: Magnetic resonance angiograms, OCT: Optical coherence tomography, NOTB: Neuro-oncology tumour board, STR: Subtotal resection, GTR: Gross total resection, IMRT: Intensity-modulated radiation therapy, VMAT: Volumetric modulated arc therapy, 3D-CRT: Three-dimensional conformal radiation therapy.

studies prefer gross total resection, there are others that show that subtotal resection followed by radiation therapy leads to better outcomes. However, radiation therapy is also associated with complications such as cognitive deficits, vasculopathy, and the development of a secondary tumour.[41]

Craniopharyngioma can itself present with endocrine abnormalities. However, it may also be a result of the treatment (surgery, radiosurgery, radiotherapy).[37] There is significant evidence of hypothalamic dysfunction, obesity, neurocognitive decline, reduced quality of life, and mortality occurring secondary to the treatment.[56, 57]

Gaps in knowledge

In LMICs, the unavailability of a multidisciplinary team in tertiary care centers is the most important impediment of better management in patients with craniopharyngioma.[58] Further, the lack of resources such as proper pre-surgical care facilities and imaging modalities, surgical equipment, post-surgical intensive care units further increase the burden of management. Delayed presentation and massive tumour burden also leads to poor outcomes due to significant post treatment complications. No insurance and unavailability of tertiary care centers with multidisciplinary teams will make it difficult for families and patients to continue regular follow ups.[59, 60] All these factors have contributed to a limited literature on the outcomes and management of craniopharyngioma, especially from LMICs.

Conclusion

Created to assist doctors practicing in areas with limited resources, these guidelines offer a pragmatic framework derived from valuable expertise (refer to Table 1 and Figure 1). Applying these guidelines could substantially enhance specific results and encourage a greater focus on collaborative care in low- and middle-income countries (LMICs) like Pakistan.

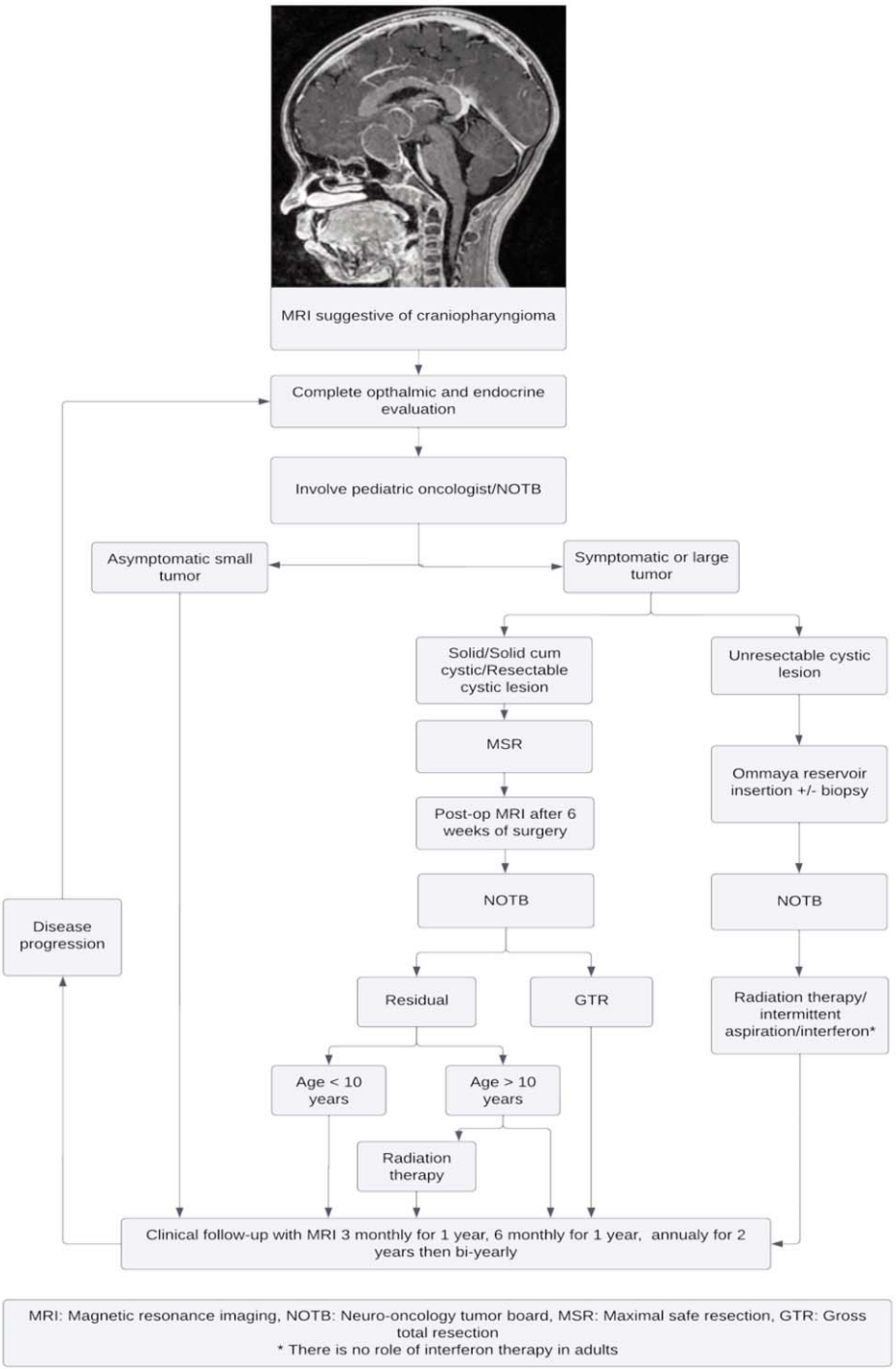

Figure-1: Management of craniopharyngioma algorithm.

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