

# Craniopharyngioma

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**Abstract:** Craniopharyngiomas (cranio = skull, pharynx = throat, oma = tumour) are benign tumours with a malignant clinical course and are a formidable challenge to the neurosurgeon and his expertise. They have a bimodal pattern of occurrence and present with visual and endocrine disturbances. The clinical pattern varies between the adult and the child. They are easily detected on x-ray, CT and MRI. In spite of its recognition in the late 1800s, no clear consensus has been reached with regards to its treatment. Philosophy of treatment is not only different among different surgeons but also in the span of a surgeon's career. (p1-9)

**Key words:** Craniopharyngioma, Rathke cleft/ pouch tumours, hypophyseal duct tumours and adamantinomas

## Introduction

Craniopharyngiomas are slow-growing, benign, locally invasive intracranial tumours that can generate considerable morbidity and recurrences are often difficult to manage. As reliable morphologic criteria for accurately predicting the clinical outcome of these tumours is lacking, it has challenged the neurosurgeon and his skills for years. These tumours have a very intricate relation with the hypothalamus, pituitary stalk and optic apparatus, which have caused excessive problems regarding optimal management. Even now, no consensus exists in the optimal management of these patients.

## Historical review

Zenker, in 1857, recognized a suprasellar cholesterol containing lesion at autopsy. Onanoff, in 1892, coined the term *pituitary adamantinoma* for these lesions. Mott and Barrett, in 1899, postulated that these tumours arose from the hypophyseal duct. Halstead, in 1909, excised a craniopharyngioma through trans-sphenoidal route. McKenzie, in 1924, termed this lesion *craniopharyngeal pouch tumours*. Cushing, used the term *craniopharyngioma*, for these lesions. The other names for this lesion are *ameloblastoma*, *epidermoid tumour*, *craniopharyngeal fat tumour*, etc.

## Embryology

In the fourth week of gestation, invagination of the epithelial cells of the stomodeum takes place. The upward migration of epithelial cells is intercepted by the neuro epithelium of hypothalamus. The upward migration forms the Rathke's pouch and the downward growth forms the neurohypophysis. The migration from the oral cavity is called *craniopharyngeal duct*. The embryonic rest cells from the craniopharyngeal duct are responsible for the development of craniopharyngioma. The craniopharyngeal duct theory was challenged after 10 years. The second proposed theory says that the existing rest cells of the adenohypophysis undergo metaplasia. Arguments against this theory are based on the mixed tumours, demonstrating papillary squamous and adamantinomatous characteristics. Since controversies still exist dual theory is supported by another group, who believe these tumours are a single entity, within a broad spectrum of neoplasia.

## Epidemiology

They form up to 12% in paediatric brain tumours and 7 - 9% of all intracranial tumours. Thirty-five percent of them are younger than 20 years. Of these, 60% are less than 16 years. There is also a bimodal incidence with the highest incidence between 5 - 15 years and those between 50 and 75 years, which gives a basis for hypothesizing a different pathophysiology for children and adults.<sup>12</sup> The geographic incidence also exists, with the highest incidence in Africa, and in America, with the least in Australia - 1.5%. Moderate incidence is seen in Asian countries - 6 to 7%. The incidence in both the sexes are equal, however, it is more common in males by 30%, in several European series.<sup>3</sup>

## Neuro-imaging

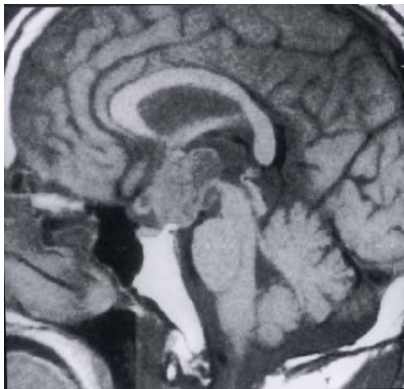
Skull radiographs are abnormal in about 95% of children and 70% in adults. The sella is enlarged or eroded in 50% of cases. Calcification is seen in 40% of adult x-rays and

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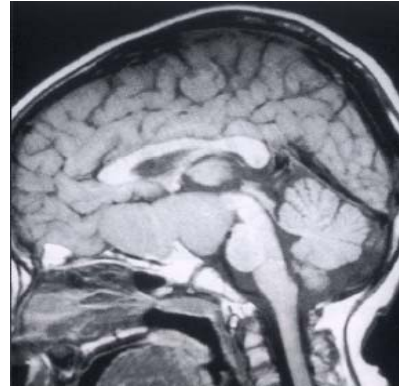
85% in children, which is a characteristic feature. Recent evidence points to presence of calcification, even in papillary squamous tumours. Computed tomography (CT) scan usually displays calcification and the cyst may be hypodense or hyperdense or with variable density, the cyst is related to anatomical structures like pituitary gland, optic nerve, optic chiasma or the optic tract, third ventricle and other major intracranial vessels (Fig. 1). The capsule usually enhances to contrast. Magnetic resonance imaging (MRI) scans usually do not pick up minor calcifications.<sup>16</sup>



**Figure 1** - Tumour extending to the 3rd ventricle

Depending on the contents of the cyst (*protein, cholesterol, triglycerides, methemoglobin or desquamated epithelium*), the intensity varies. On T1-weighted images, there is a hyperintense signal, especially if the protein concentrations are more than 90 grams per litre. The solid component is homogeneously hypointense in T1-weighted images and hyperintense on T2-weighted images. Hyperintensity on T1-weighted images represents old bleed, as also hypointensity on T2-weighted images (*haemosiderin and caratin*). Solid areas intensely and homogeneously enhance with *gadolinium*. The tumours may be homogeneous or heterogeneous or both, depending on the predominance of the cystic or the solid component.<sup>25</sup> Only a minority are entirely cystic or entirely solid. In relation to the optic apparatus, 60% have an intrasellar component, with 60% of the tumours having suprasellar extension, with or without a retrosellar, parasellar extension and about 40 - 45% having posterior fossa extension (Fig. 2).<sup>26</sup> Ectopic lesions are rarely formed in the cerebellopontine angle, pineal region, paranasal sinuses and nasopharynx. Radiological and histological co-relations, to predict the behaviour of the tumours are done. The idea being the lesions with the papillary variant are less aggressive than the adamantinomatous variety. Lack of calcification predicts a better survival rate. Cystic component is more common in the adamantinomatous type. The papillary type has an inhomogeneous

enhancement and the adamantinomatous type is more invasive, encroaching on the subarachnoid vessels and shows hyperintensity on T1-weighted image.



**Figure 2** - Tumour extending into anterior cranial fossa

### Clinical presentation

The symptoms reflect the location of the lesion and the proximity to the structures like optic apparatus, hypo-thalamo-pituitary axis, the ventricles, the suprasellar, parasellar, infrasellar or with retrosellar involvement. Endocrine disturbances appear with involvement of hypothalamo pituitary axis and symptoms of raised ICP appear with ventricular involvement. Likewise, brainstem functions are disturbed with a retrosellar growth. Children, more often present with features of raised ICP and ventriculomegaly, whereas adults present with visual and endocrine problems.<sup>30</sup> Eighty percent of adults have visual involvement, due to involvement of different parts of the optic apparatus (*nerve, chiasma or tract*). The presentation may be bi-temporal hemianopia, unilateral hemianopia, partial or total blindness. The evidence of papilloedema is much less in adults (25%) compared to children (60 - 70%).<sup>4</sup>

### Visual disturbances, endocrinologic deficits and other features

Most common deficit is a loss of libido, reduced masculinity and gonadal insufficiency in men and dysmenorrhea or amenorrhea, hyperprolactinemia, adrenal and thyroid insufficiency, in women. Diabetes insipidus appears in both sexes. The children remarkably have much less endocrine problems, the most common being a reduced growth hormone, with short stature, delayed puberty and other features of polyurea and polydypsia. The hyperphagia with obesity, disturbance in the satiety centre and sleep cycles are more common in children, than in adults. The blood level for adrenocorticotrophic hormone, thyrotropin-releasing hormone, gonadotropic-releasing hormone, growth hormone and cortisol levels are checked, both in the base line and

stimulated states, to assess the endocrinologic status. The raised ICP is due to upward migration into the third ventricle with resultant hydrocephalus, which is seen more in children but the neuro-behavioural abnormalities are more common in adults, which include features of intermittent confusion, hypersomnia, depression and apathy. Psycho-motor retardation and cognitive decline, is more common in children. Rupture, haemorrhage, aseptic meningitis are other presentations as complications in this lesion.<sup>38</sup> Leak from the nasopharynx is extremely rare.

### Pathology

Craniopharyngiomas are epithelial neoplasms usually located in the sellar and suprasellar regions. Distinguishing craniopharyngioma from Rathke's cleft cyst is sometimes difficult and the distinction is clinically significant because Rathke cleft cysts have a better prognosis than craniopharyngiomas. The paediatric population in more than 95% have adamantinomatous variety, whereas papillary variant, is more common in adults.

**Adamantinomatous craniopharyngioma:** These lesions are more often in the suprasellar area and adhere to the adjacent vessels and compress the floor of the third ventricle. They are typically called "Crank Case Oil / Machine Oil Like fluid", due to cholesterol droplets. Necrotic debris and keratin are also found. They have a layer of columnar epithelial cells around a central area, appearing like a clover leaf. The epithelial cells are neoplastic and resemble tumours of dentine origin and hence the name adamantinomatous. The epithelial cells regress and accumulate debris, giving a characteristic wet keratin appearance and undergo dystrophic calcification. These tumours may or may not have a definitive demarcation with normal neural structures and may involve the hypothalamus, microscopically.

**Papillary craniopharyngioma:** They are usually solid, invasive and enclose vascular structures. They have a well differentiated squamous epithelium, with a fibro-vascular stroma. Sheets of cells, along the fissures give a papillary appearance. It is similar to an epidermoid on gross appearance. There are no cholesterol droplets, wet keratin or palisading cells. The monoclonal antibody (*Ki-67*) and bromideoxyuridine labeling show a very low proliferative index, which serves as a marker to assess recurrence. Oestrogen and progesterone receptor mRNA are present in the craniopharyngiomas, suggesting a hormone related pattern. Immunostaining for cytokeratin is valuable in the investigation of craniopharyngioma, especially when specimens contain only a small or questionable part of epithelium. Most notably, KL-1 or cytokeratin<sup>(11)</sup> stainings are suitable for analyzing these tumours, with special reference to histological subtypes.<sup>1,15,37,38</sup>

### Classification system

The anatomical location and the growth pattern with the imaging and intra-operative findings and involvement of the surrounding adjacent structures are utilized in classifying these lesions. Various methods of classification by different authors were used like giant and small, typical and atypical, retro, sub or pre-chiasmatic, intra, supra, para and retro sellar varieties. It was Yasargil, who categorized these tumours as Types A to F.<sup>6</sup>

- Type A - intrasellar - infradiaphragmatic
- Type B - intra and suprasellar, infra and supra diaphragmatic
- Type C - supra diaphragmatic, parachiasmatic, extra ventricular
- Type D - intra and extra ventricular
- Type E - purely intraventricular
- Type F - extra dural and extra cranial

Giant tumours have a diameter of more than 5 cms, are cystic and extend into either fossa. The relationship to the chiasm and the optic apparatus determine a pre-fixed or a post-fixed variety. Usually pre-chiasmatic lesions grow to a large extent. The lesions are supplied by anterior cerebral, anterior communicating and posterior communicating arteries. The hypophysial vessels supply the intrasellar area.<sup>37</sup> They usually do not receive blood supply from posterior circulation.

### Investigations and management

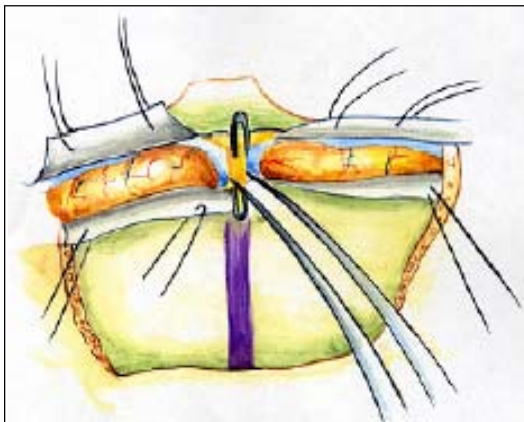
In the preoperative phase, apart from the evaluation for the symptoms, the endocrinological and the visual workup are mandatory. Complete pituitary function tests, water deprivation test, visual acuity fundus exam, visual field test, skull radiographs, CT and MRI with contrast are necessary apart from the management for hydrocephalus. The philosophy of treatment has vacillated in the last fifty years. Initial series demonstrate a very high mortality rate and a low total excision rate. In the next decade, surgeons felt aggressive therapy should be abandoned and radiotherapy was favoured. In the mid-1970s, with improved surgical techniques, instrumentation, endocrine knowledge etc., an aggressive surgical approach was instituted. Even today, there is no actual consensus regarding definitive management. The histology being benign, led to the conclusion that they need to be totally excised but it is an aggressive surgical approach that can inflict irreparable damage, with significant morbidity, due to neurovascular involvement. Therefore, many philosophies in the management are still under survey. It is a combination of the patient, the symptoms, signs, imaging, clinico-radiological co-relation, follow-up and to a certain extent, the surgeon's attitude, that determines the management strategy. A single tumour may be approached by different surgeons in a variety of ways, which depends on the location of the tumour, the size, shape, extent,

consistency, percentage of solid and cystic component and the surgeon's anatomical knowledge. Various surgical approaches like unilateral sub-frontal, bi-frontal interhemispheric, pterional, temporal or sub-temporal, trans-sphenoidal, trans-ventricular or trans-callosal, may be considered in approaching this tumour.

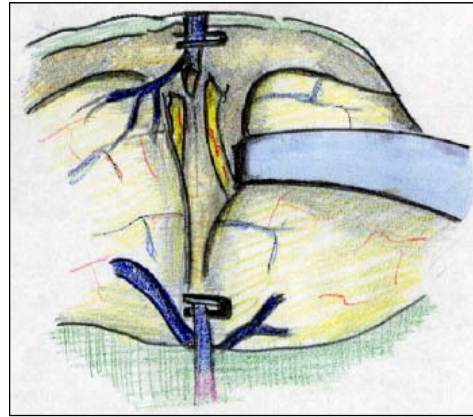
By and large, a sub-frontal approach is most commonly used, with a bi-coronal flap being made (Fig. 3). The pericranium is carefully reflected and a unilateral or a bi-lateral frontal craniotomy is performed. The sinus is dealt with by extracting the mucosa and packing it with fat and muscle. The pericranial flap may be used to cover the sinus, to prevent a CSF leak. After dural opening, the frontal lobes are retracted with care to preserve the olfactory tract and the bridging veins (Figs. 4 and 5). The most important step here is to separate the interhemispheric fissure carefully. Only one of the bridging veins may be sacrificed if necessary. If more than one vein is injured there is a chance of a venous haemorrhagic infarct which may delay the postoperative recovery of the patient (Fig. 6).



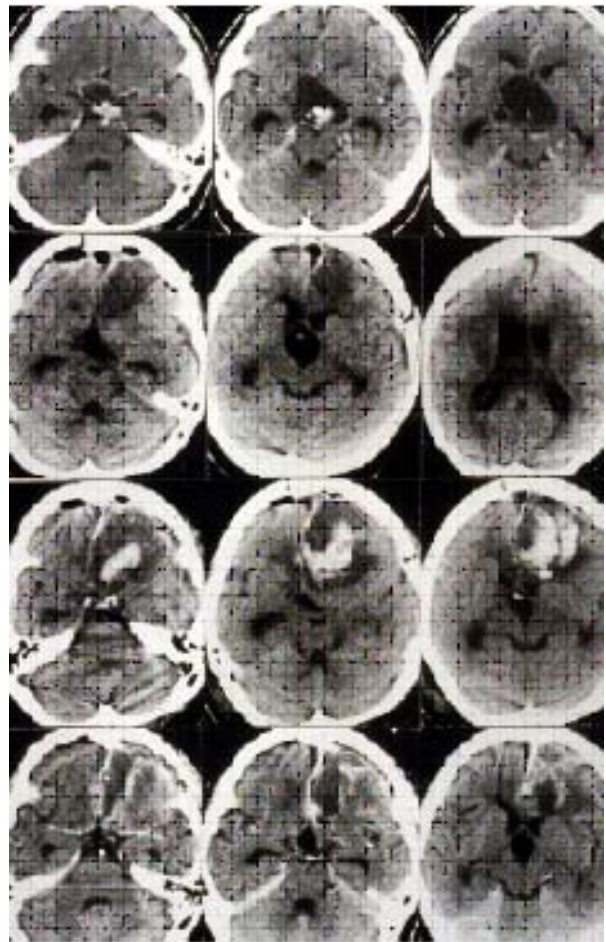
**Figure 3** - Bifrontal craniotomy is performed as done for anterior skull base tumours



**Figure 4** - Only one of the bridging veins can be sacrificed



**Figure 5** - Retraction may cause injury to the bridging veins



**Figure 6** - Haemorrhagic infarction

The olfactory tract can very easily be damaged and proper care must be taken to prevent tear, traction and retraction along with the frontal lobes. It can actually be preserved if the surgeon is alert and watchful and in fact, use of glue like

bio-bond oxycell can help retain the nerve both anatomically and functionally (Fig. 7). Pre-chiasmatic and carotid cisterns are opened to relax the brain. The optic apparatus and internal carotid artery is visualized. The sub-chiasmatic portion of the lesion is debulked and then the supra-chiasmatic part is dealt with (Fig. 8). The tumour is reflected from the anterior to the posterior region and this goes a long way in preventing damage to the perforating arteries. The perforators (Fig. 9) should be zealously protected, lest the hypothalamus is damaged and the patient may have a very unpredictable postoperative course.



Figure 7 - Protection of the olfactory tract by glue

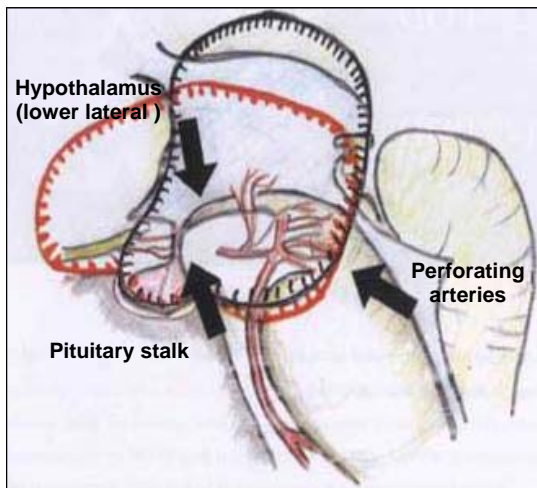


Figure 8 - Important relations

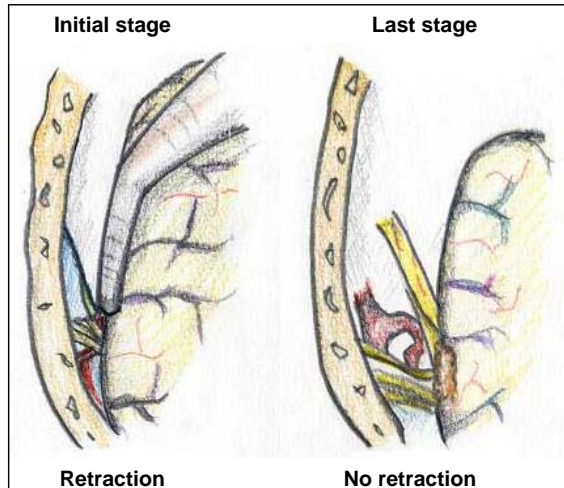


Figure 9 - The initial and last stage with and without retraction

In a prefixed chiasm the tumour is retro-chiasmatic and requires a lamina terminalis approach. The lamina terminalis is incised below the anterior communicating vessels and the tumour excised. Intra-sellar portion can be excised by drilling the tuberculum sellae and avoiding injury to the sphenoidal sinus mucosa (Fig. 10). More often, the lesion cannot be completely excised due to its dense adherence to the hypothalamus and neurovascular structures which should be preserved at all cost (Fig. 11).<sup>27,39</sup> Another important structure to be preserved is the posterior pituitary and the stalk of the pituitary. This is usually where the tumour arises from and leaving a little more of the pituitary stalk invites definite early recurrence and overzealous resection causes severe diabetes insipidus. The surgeon should decide according to the merits of the case and then embark upon a decision in overcoming this dilemma. The third nerve in the region of the pre-pontine area should be protected to prevent palsy. After a satisfactory total removal the surgeon should be able to see the intact arachnoid, the

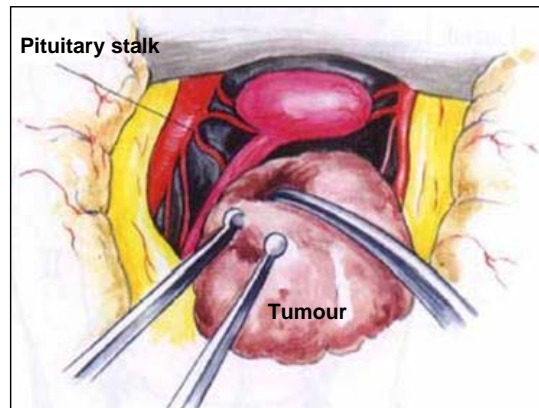


Figure 10 - Relation of pituitary stalk with tumour

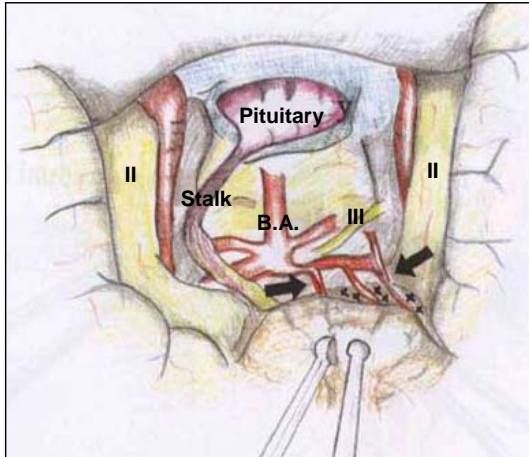


Figure 11 - Preservation of the posterior perforators

vertebral, superior cerebellar and the posterior cerebral vessels (Fig. 9).

Large midline retro-chiasmatic tumours with retrosellar extension can be dealt by bi-frontal, basal, inter hemispheric approach. This causes danger to both the frontal lobes and the anterior communicating vessels (Figs. 3 and 12).

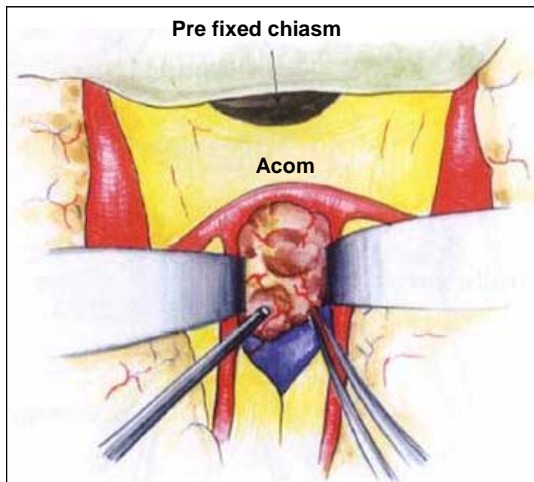


Figure 12 - Tumour in relation to a pre-fixed chiasm

More often, pterional approach is used, due to the anatomical familiarity and shortest route, to the sellar and the parasellar area. The clinoid is drilled and the opticocarotid space is dissected to excise the lesion. Large retrochiasmatic and retrosellar lesions are difficult to excise through this approach.

Unilateral predominantly retrochiasmatic lesions can be approached, sub-temporally. Two centimeters of the temporal lobe needs to be resected, along with the uncus and the

lesion approached through a transsylvian route, through the interpeduncular cistern.<sup>7</sup>

An intrasellar lesion, with or without a suprasellar extension, and predominantly cystic lesions can be approached trans-sphenoidally. The pituitary is displaced anteriorly and needs to be incised to approach the lesion completely. This route harbours a problem of CSF rhinorrhea.<sup>5</sup>

Lesions in the upper third ventricle can be approached by a parasagittal craniotomy through a trans-frontal corticectomy. The transcallosal approach may be used and tumour delivered through the third or the fourth ventricle (Figs. 13 and 14). The lesion is relatively easier to remove as it is not adherent to any important structures with the tumour in relation to the third ventricle at the posterior aspect.

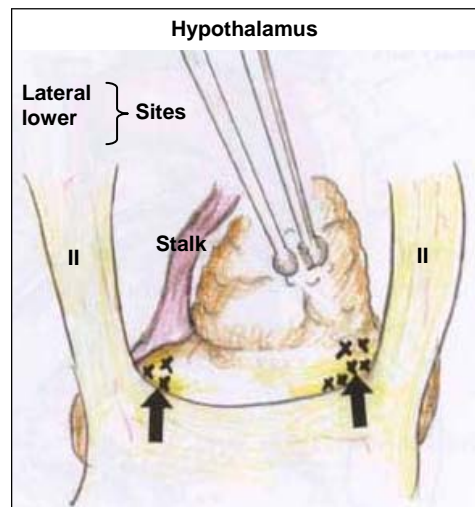


Figure 13 - Relation to the hypothalamus

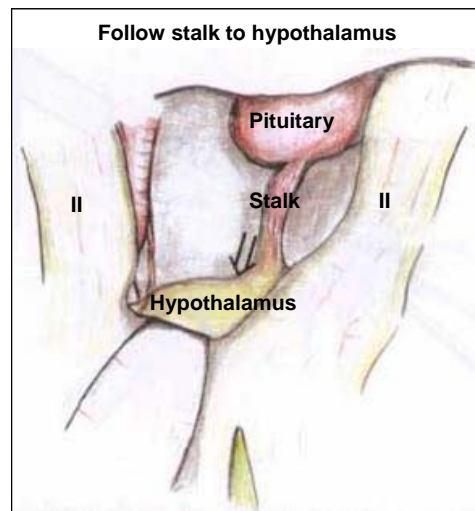


Figure 14 - Pituitary stalk traced to the hypothalamus

Less invasive approaches include a decompression of the cyst alone and a stereotactic aspiration to relieve the symptoms temporarily. The cyst may be connected to an Omayya reservoir and intracavitary chemoradiotherapy administered.<sup>21</sup>

## Results

By and large, aggressive resection gives a better chance for cure. The extent of resection and the recurrence of the lesion depend on the size, site, the architecture, tumour behaviour etc., and the neurosurgeon's attitude, towards resection. The MRI studies have proved the surgeon's intra-operative total resection as being false, with the advent of the newer imaging methods. The mortality is related to the aggressiveness of the surgery and the preoperative condition of the patient. Up to 5% immediate surgical mortality and 15% first year surgical mortality can be expected due to hypothalamic damage. A 40 - 90%, 10-year survival rate is published in the literature but a large variation actually exists.<sup>14</sup> Overall, mortality is more in females than in males by 3 times.<sup>29,34</sup>

Morbidity in relation to the visual outcome, is variable, and depends on the aggressiveness of the surgical resection and preoperative visual deficits and the tumour relation to the optic apparatus. The sub-total resection also has an equivalent visual outcome. Endocrine morbidity is seen in more than 80%, more common being diabetes insipidus in the immediate postoperative period in 80% of the patients. Disturbance of the pituitary stalk always causes endocrine involvement and it is less likely with a transsphenoidal excision. Hypogonadism, growth hormone deficiency, hypothyroidism, hyperprolactinemia and secondary adrenal dysfunction, is seen in 25 - 45%.

Radical resection is likely to cause neuropsychological disturbances and frontal lobe dysfunction, with a reduced Karnofsky performance score. Vascular complications due to adventitial damage occur in the carotid vessels, resulting in cerebral ischemia.

## Recurrence

Recurrence rates depend on the surgical resection, adjuvant radiotherapy, tumour infiltration, relationship to pituitary stalk and the histopathology. Complete stalk resection points to a lower incidence of recurrence and increased endocrine deficiency. The papillary varieties in certain studies are prone to more recurrence than the adamantinomatous variety. Tumour location was the single significant clinical predictor of recurrence and is usually at the primary or contiguous sites. The most frequent sites of recurrence are optic nerve/chiasm and the pituitary fossa (Figs. 15 and 16). Ectopic recurrence in proximal Sylvian fissure has also been reported. Seventy percent undergoing craniotomy can have a complete resection. This depends

on the surgeon's dexterity. Large number of studies report 70% recurrence in sub-total resections. Tumours less than 2 cms can usually be resected rather than tumours more than 4 cms.

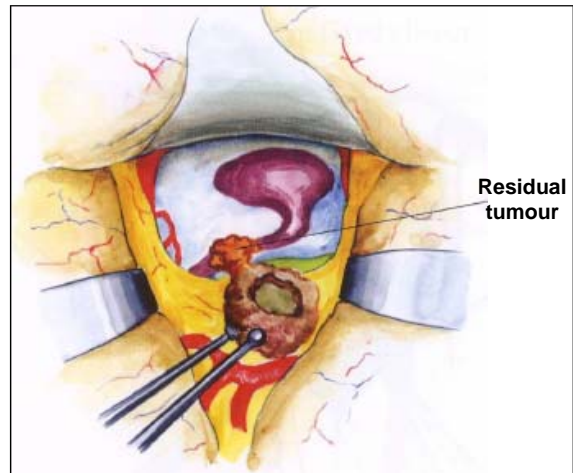


Figure 15 - Residual tumour at the stalk left behind

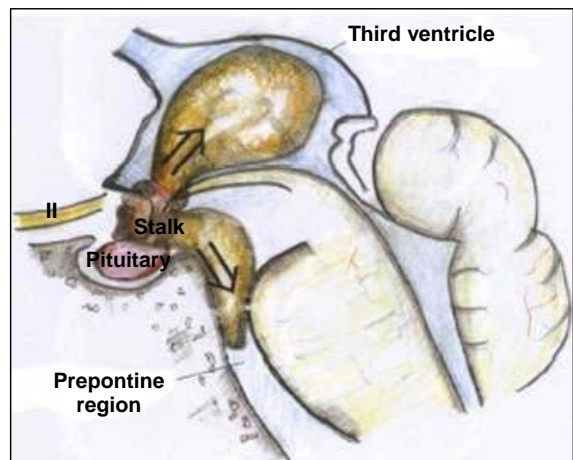


Figure 16 - Extension of the recurrent lesion at the stalk

## Radiotherapy and chemotherapy

Complete surgical control of the growth in craniopharyngiomas is not possible and hence, radiotherapy has taken a prominent role in the management. The lack of authority in the studies gives doubt about the overall benefits of radiotherapy. The risk of recurrence for subtotal resections, treated with adjuvant radiation, is in the order of 15 - 30%. The progression free survival is in the order of 80 - 85% at 10 years. Different series of studies have different opinions in management strategy with radiotherapy. Several studies have reported acute deterioration at the time of radiotherapy, with visual problems and hydrocephalus.<sup>19</sup> Optic

nerve injury, radiation necrosis, pituitary dysfunction and radiation induced dementia are side effects of this treatment. Radioisotopes like phosphorous 32 and yttrium 90 have been placed in the cystic cavity as a means of intracavitary radiation as a mode of combination therapy to achieve long-term disease free survival and possible cure. Studies show a 50% reduction in 90% of the subjects. Thirty percent suffer from visual dysfunction with intra cavitory treatment. Other radiosurgical techniques like stereotactic radiosurgery with Linac or Gamma Knife, have precisely defined the application of radiation with sparing of the brainstem and optic apparatus. Fractionation can also be applied to limit optic nerve injury and overall toxicity.<sup>22</sup> In treating recurrent or residual craniopharyngiomas, if further microsurgical excision cannot promise a cure, this multimodality management seems to provide a better quality of patient survival and greater long-term tumour control. Intracavitary chemotherapeutic agents like bleomycin have been used which causes DNA damage of the tumor cells.<sup>11</sup> It is administered via reservoir and the treatment lasts for a week with 50% of the patients demonstrating complete disappearance of the tumour cyst. It is also administered in weekly regimes.

### Conclusion

Craniopharyngiomas are very difficult tumours to treat. Their benign histology is misleading. These tumours test the dexterity of the surgeon, the clinical skills and neurosurgical expertise, in all dimensions. Care must be taken, when attempting complete resection. Potential surgical morbidity and probably mortality can occur, many a time. The ability to resect the lesion is not the only criteria to be considered. Selection of cases, judicious administration of radiotherapy or chemotherapy must be judged and tailor-made to every case. Rigorous evaluation must consider not only the extent of resection, as judged by postoperative imaging, but also the long-term physical, intellectual, and psychological functioning of the patients.

### Acknowledgement

All the staff, doctors, medical and paramedical personnel and the patients of the Department of Neurosurgery, Fujita Health University Hospital.

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## GENTLE REMINDER

### Differential diagnosis of supratentorial paediatric brain tumours

Cerebral Hemispheres	
Superficial (including meninges) (37%) Meningioma Desmoplastic astrocytoma Desmoplastic infantile ganglioglioma Dysembryoplastic neuroepithelial tumour Pleomorphic xanthoastrocytoma Others Haemangiopericytoma Malignant fibrous histiocytoma Mesenchymal chondrosarcoma Metastatic	Deep (including vassal ganglia, thalami) (10%) Pilocytic astrocytoma Primitive neuroectodermal tumour Ganglioglioma Diffuse fibrillary astrocytoma Gangliocytoma Oligodendroglioma Atypical teratoid / rhabdoid tumour Lymphoma Others, germinoma
Suprasellar (40%)	Intraventricular (3%)
Craniopharyngioma Germ-cell tumours (germinoma) Astrocytoma (optic nevus, hypothalamus) Hypothalamic hamartoma Pituitary adenoma Gangliocytoma Langerhans' cell histiocytosis Lipoma Meningioma Cysts, arachnoid, Rathke cleft, epidermoid	Choroid plexus papilloma / carcinoma Ependymoma Subependymal giant-cell tumour Colloid cyst Oligodendroglioma Astrocytoma Neurocytoma Meningioma
Pineal (10%)	
Germ-cell tumours Pineoblastoma Astrocytoma Pineocytoma Atypical teratoid / rhabdoid tumour Ependymoma Meningioma Melanoma Lipoma Cysts, pineal, arachnoid	