Commentary

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Evolution of concepts in the management of craniopharyngiomas: Lessons learnt from Prof. S.N. Bhagwati's article published in 1993

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Craniopharyngiomas are slow-growing benign tumours that have their origin from embryonic squamous cell rests of an incompletely involuted hypophyseal-pharyngeal duct. The sellar and suprasellar region is a site of intense and precise actions in the first trimester, wherein the formation of adenohypophysis and neurohypophysis takes place in a definite sequence. Some of the cell rests can be found in the sella, suprasellar region, pituitary stalk, third ventricle and posterior pharyngeal wall. Erdheim's report was the first to document that the tumour arose from squamous cell rests.[1] A craniopharyngioma can develop at any of the sites along the hypophyseal-pharyngeal duct, and depending on its growth, can manifest with visual loss, optic atrophy, growth disturbances, feeding and endocrinological problems, disturbances in sexual function and multiple cranial nerve palsy. Some of the papers that have appeared in the last two decades have reviewed the origin and pathogenesis of these tumours.[2,3]

Few tumours have been subject of such an intense debate as craniopharyngiomas. Approaches to these tumours have also been intensely scrutinized, adapted and projected. Notwithstanding their benign histology, the tumour is locally invasive and a number of vital structures around it are vulnerable, either by the tumour extension, or by attempts to excise it. Pioneering attempts at excision that left the patients severely compromised, made the master neurosurgeon Harvey Cushing[4] comment:

"Craniopharyngioma offers the most baffling problem which confronts the neurosurgeon. It has always proved a challenging and a frustrating tumour to the neurological surgeons, because, despite its benign nature, histologically, there have been almost insurmountable technical and physiological difficulties incident to its surgical manipulation….

…One would expect these congenital epithelial tumours to be capable of enucleation like dermoid cysts elsewhere in the body, but they so definitely adhere to the adjacent structures neighbouring on their place of origin, it is rarely possible to shell them out of their bed without the production of serious secondary symptoms. To be sure, one may occasionally succeed in stripping out a thin-walled cyst, and examples of this have been reported, but when the tumour is partly solidified and calcareous, sad experience warns the surgeon to leave it pretty much alone."

Recurrence may follow even after seemingly total surgical excision, corroborated by postoperative imaging. Due to their tendency to recur, and the neuroendocrinological and visual complications associated with them, there have been serious considerations for 'safe' resection followed by the administration of non-surgical measures, notably irradiation and intracavitary instillation of radioisotopes. Radiation therapy has brought forth its deleterious effects on the growing brain, with learning and quality-of-life issues. The operating microscope, and now the neuroendoscope has made surgery more refined, with better visualization of dissection planes. Availability of hormone replacement therapy can embolden the surgeon to be radical while excising the tumour. With the transbasal and endoscopic procedures gradually gaining acceptance, craniopharyngiomas can be excised practically by the 360° perimeter with the tumour being the center.

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The Article

The first consolidated experience with surgery for craniopharyngiomas from India appeared in a supplement to Neurology India in 1991, which contained eloquent descriptions on surgical management by Deopujari and Bhagwati, AK Banerji, Rout *et al*., Dharker *et al*., Venkatramna *et al*., and Bhagwati. All these studies emphasise the importance of preoperative evaluation by imaging and planning the surgical approach. Banerji recognized that most of the tumours were retrochiasmal [Figure 1].[5]

Prof SN Bhagwati (SNB) was a pioneer in the then nascent field of Pediatric Neurosurgery. His Presidential Oration at the Annual Conference of Neurological Society of India Conference on Craniopharyngioma was published in Neurology India in 1993.[5] The article is the first report of a large series from India on the surgery and management of craniopharyngiomas.

SNB outlined the problems associated with the management of craniopharyngiomas in the introduction itself, by posing a series of questions, that remain equally relevant today. Does palliative surgery to relieve pressure on the optic pathways or to relieve hydrocephalus in such cases, postpone the inevitable only for a while? Or when combined with radiotherapy, does it help to achieve a long-term cure? How effective is radiation in arresting the further growth of these craniopharyngiomas? Are we justified in subjecting an immature or growing brain to the hazards of radiation? Do patients who have had a so-called "total excision" ever experience a recurrence? If so, how should they be treated? Does radiation render a reoperation more difficult? Is it possible to excise such a recurrence completely?

Epidemiological Background

Craniopharyngiomas are common intracranial tumours of childhood, having a prevalence rate of 6-10% of all pediatric tumours.[6] Nielsen *et al*.,[7] reviewed 15 population-based studies in the world literature and estimated a world incidence of 1.34 patients per million people. Another study from the US reported that the incidence of craniopharyngioma constituted 0.9% of all central nervous system (CNS) tumours.[8] The bimodal age distribution is well described with a peak in the pediatric age group (5-15 years) and another peak in adulthood (in the seventh decade).[9] The tumour has been reported in the prenatal period, infancy and even in the ninth decade.[10,11] Indian literature shows a prevalence rate of between 5.82% and 12.5% amongst all pediatric intracranial tumours, as reported from major institutes.[12]

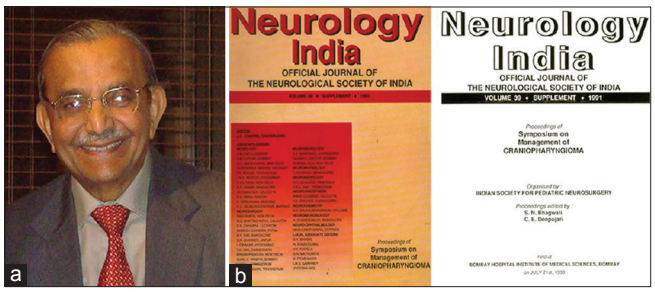

Figure 1: (a) Professor SN Bhagwati; (b) The cover page of supplement issue of Neurology India on craniopharyngioma (Reprinted with permission from the article: Deopujari CE. Neurosurgery at the Bombay Hospital. Neurol India 2017;65:600-6)

Presentation

SNB's article gives a clinically precise account of presentation of these tumours. Most of his patients were male children, while tumours in adults were more or less equally distributed among male and female subjects. Most of the patients had features of raised intracranial pressure, in the form of headache (41/56) and vomiting (37/56), followed by failing vision (34/56). Endocrinopathy in the form of stunted growth (11/37 children) and obesity (3/37 children) were the next common modes of presentation. Six out of 56 patients had diabetes insipidus at the time of presentation. The duration of symptoms averaged about six months in most of the patients. There were a few patients with uncommon neurological manifestations also. While it is universally accepted that treatment is sought predominantly for headache and visual symptoms, nearly 80-90% percent of these children will have an endocrinological deficiency; only 7% will complain of short stature, while 50-60% will have stunted growth on examination.[13] One fourth of them will be obese, and majority of the adolescent patients will have a pubertal delay.[13] A rare presentation in the form of emaciation and diencephalic syndrome too has been reported.[14]

Imaging

In SNB's article, a skull radiograph was done in all the patients, which revealed a sellar or suprasellar calcification in 83.3% of children and 40.0% of adults. In the pre-computed tomographic (CT) scan era, 22 patients had either pneumoencephalography or ventriculography prior to definitive surgery. The CT scan was the main imaging modality in 34 patients. Imaging is a field with a remarkably changed landscape in the evaluation of craniopharyngiomas. On a CT scan, a craniopharyngioma can be diagnosed with certainty in a child having a suprasellar cystic tumour with calcification. The CT scan shows calcification in tumors in 90% children and in 70% adults.[15] MRI (magnetic resonance imaging) is the imaging modality of choice, and the striking MRI features are the presence of the typical cysts, hyperintense on T1-weighted images, due to the contained "machine-oil" fluid being rich in protein and cholesterol. The papillary type is more often solid, and less calcified.[16] Solid portions and the margins of the cyst show uniform contrast enhancement on T1-weighted imaging. The T2-weighted and fluid attenuated inversion recovery (FLAIR) images show hyperintense cysts with a heterogenous solid portion [Figures 2A-D].

The FLAIR image is useful in defining the cystic portions of tumour (which appear hyperintense) and help to differentiate them from loculated portions of the third ventricle or other cerebrospinal fluid (CSF) spaces (which appear isointense). The gradient reversal echo (GRE) image is a susceptibility sequence that is helpful in demonstrating calcification and blood products. The diffusion weighted imaging (DWI) sequence can distinguish the tumour from an epidermoid. The MR spectroscopic image may show a significant lipid content.

The present day MRI recommendations are thin T1-weighted coronal and sagittal sections, both pre- and post contrast

through the sella and suprasellar region. It is useful to include a pre-contrast fat saturation T1-sequence as it will help to identify the "bright spot" representing the posterior pituitary gland.

MRI provides not only the diagnosis with certainty, but also gives information about the the anatomical extent, the likely anatomical structures that are affected, the degree of infiltration, the encasement of major vessels, and forms the basis for deciding the surgical corridor and treatment plan. Equally important is the postoperative evaluation [Figure 2B and D], preferably after 3 months of surgery.[17]

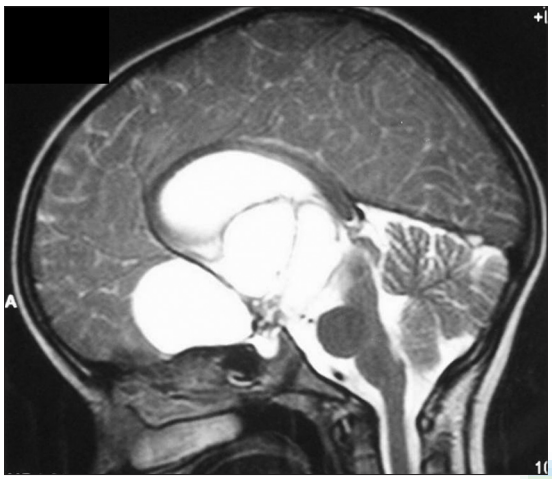

Figure 2A: Patient 1: Multicompartmental craniopharyngioma seen on sagittal T2-weighted MRI brain

Tumour size and configuration

Anatomically and topographically, the most frequent type of the tumour is located in the suprasellar region, with an intrasellar component. According to Harwood Nash *et al*.,[18] about 5% of the tumours are intrasellar, 20% are restricted to the suprasellar region, 30% have an anterior extension, 23% have an extension into the middle fossa, and 20% have a retrosellar extension.

Majority of the tumours (39/56 or 69.6%) in SNB's series were large (size 3-5 cm). Giant craniopharyngiomas (size >5 cm) were seen in 14 (25%) patients, while 3 were medium-sized tumours (size 1.5-3 cm or 5.3%). Eighteen (32.1%) of these tumours were cystic, 29 (51.8%) were mixed, and the rest (16%) were solid. In a series of 66 children, Puget *et al*.,[19] reported 10% purely cystic, and 20% giant tumours. In a series of largely adult patients (118 out of 148 patients), Fahlbusch *et al*.,[17] reported more than 85% of the tumours to be less than 4 cm in size and only 3.4% were purely cystic. Majority of the tumours were of a mixed type, and the overall incidence of tumour calcification was 57.4%, while in childhood craniopharyngiomas, calcification was seen in 83.3% of the cases.

Surgery for Craniopharyngiomas

SNB reported performing surgery in 55 patients; one patient underwent only aspiration of the cyst. Majority of

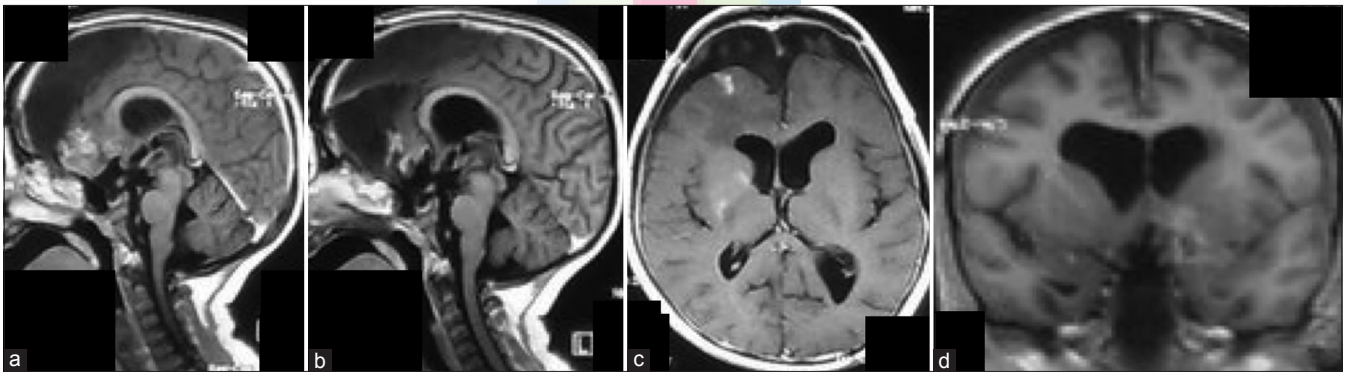

Figure 2B: Patient 1: Postoperative MRI T1 weighted image (a and b: sagittal; c: axial; d: coronal) showing minimal residual tumour

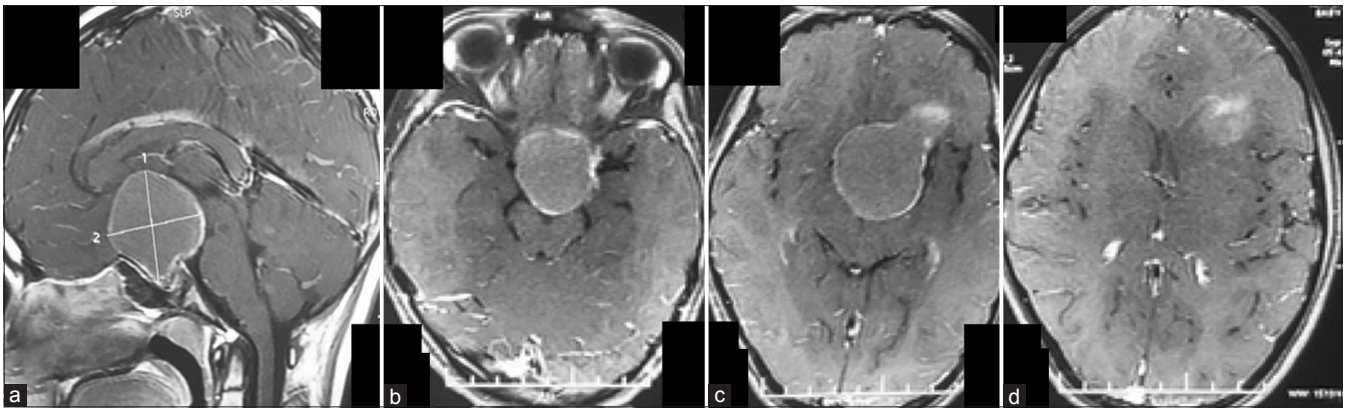

Figure 2C: Patient 2: (a-d) Sellar, suprasellar and retrosellar craniopharyngioma seen on T1-weighted contrast sagittal MRI images

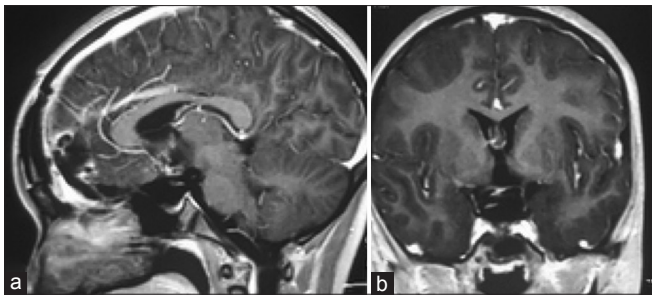

Figure 2D: Patient 2: T1 contrast enhanced (a) Sagittal and (b) Coronal MR images showing the postoperative appearance after total tumour excision

the patients (43/55) underwent surgery by the subfrontal approach. Other approaches were pterional in 3, transcallosal in 2, transventricular in 3 and subtemporal in 2 patients. Preoperative CSF diversion was carried out by the insertion of a shunt in 5 patients whereas 1 underwent an external ventricular drainage. Postoperative shunting was needed in 5 and external ventricular drainage in 2 patients. No patient underwent a transnasal-transsphenoidal surgery, probably because none of the tumours were small enough to be removable by this approach. Twelve patients had a prefixed chiasm, requiring lamina terminalis opening in eight and excision of the tumour through the optico-carotid corridor in four patients. Fourteen patients underwent total excision during the first surgery, while 23 required a second surgery due to recurrence. One patient required three, and one required four surgeries, owing to recurrence of the tumour.

Some large series have appeared in literature over the years describing various approaches, tempering aggressiveness with preoperative assessment of the degree of hypothalamic involvement, with some series reporting satisfactory outcomes after transnasal approaches for large tumours. In the retrospective study of Fahlbusch *et al*.,[17] in 148 patients undergoing initial (primary) surgery, the pterional approach was most frequently used trajectory (39. 2%) followed by the transsphenoidal approach (23.6%). For large retrochiasmatic craniopharyngiomas, the bifrontal interhemispheric approach was increasingly preferred over the pterional approach and led to improved surgical results. Total tumour removal was accomplished in 45.7% of transcranial and 85.7% of transsphenoidal procedures. The main reasons for incomplete removal were attachment and/or infiltration of the hypothalamus, major calcifications, and attachment to vascular structures.[17-19] Bakhsheshian *et al*.,[20] analyzed a large series of 1961 children operated by the cranial as well as the transsphenoidal route, and reported an inpatient mortality of 0.5%. Using multiplanar neuroimaging, one can make a treatment plan suitable and tailored for the particular patient, child or adult, so as to achieve gross total resection, or maximal resection while preserving the hypothalamus, visual apparatus and major vessels.[19,21] Craniopharyngiomas are extrapial tumours and remain so even as they enlarge, and even in large cases, it is possible to separate these tumours from the optic apparatus, the pituitary stalk and the arterial trunks.[22]

Adequate exposure is the *sine qua non* for any successful surgical procedure and an acceptable outcome. An adequate exposure allows the appreciation of anatomy, correlation of the abnormal anatomy to the preoperative imaging, and appreciation and analysis of the pathology. Together the information forms the basis for finalization of the treatment plan, which includes the sequence of events to approach the lesion, preservation of vital structures, causation of minimal collateral damage, tackling of the pathology, conversion of the abnormal anatomy to normal anatomy, and preempting postoperative problems. Comparison of transsphenoidal approaches to transcranial approaches is not valid, because of the inherent selection bias: smaller, intrasellar cystic tumours tend to be preferentially approached by the transsphenoidal and endoscopic techniques.[23] Surgery for a giant, multicompartmental craniopharyngioma has remained a challenge even in this decade of twenty first century. Hoffman[24] described quite succinctly, the needed surgical attitude for their management, when he stated, "… *perhaps the most important factor governing operative management of craniopharyngioma is the surgeon's attitude towards the tumour. If he or she regards the tumour as unresectable, it will be treated as such and no attempt will be made to remove it. If on the other hand, the surgeon feels that the craniopharyngioma can be totally removed, its management is likely to be successful."* The first attempt to remove these tumours is likely to be the best, while attempts to remove a previously operated and/or irradiated tumour will be difficult due to adherence of the tumour to the blood vessels, nerves and hypothalamus.[25] Thus, every attempt should be made to remove these tumours completely during the first surgery. Kawamata *et al*.,[26] described the craniopharyngioma-brain interface that has a bearing on resectibility of the tumour in contact with the hypothalamus. As per this description, Type I tumours are characterized by an encapsulated tumour with inflammation, facing a gliotic brain tissue. Type II tumours show a clear cleavage, and Type III tumours have an interdigitating tumour margin into the hypothalamus. The brain tissue layer adjoining the tumour is characterized by piloid gliosis and Rosenthal fibres.[27]

Surgical Challenges

The challenges encountered during the surgical management of craniopharyngiomas include focus on these three vital functions:

a. Vision: The challenge of vision-related morbidity is addressed by better understanding of microanatomy of the chiasma and the tumour, thus improving the surgical techniques and the acquiring of skills for the preservation of microcirculation of the optic apparatus
b. Endocrinopathy: Advances in hormonal therapy have improved the outcome. However, no hormonal replacement therapy (HRT) regime can replicate the complexity of normal physiology, and endocrine dysfunction will remain a challenge in times to come
c. Hypothalamic function: The quality of life following craniopharyngioma surgery is severely affected by behavioural dysfunction and hyperphagia.[28,29]

Surgical treatment has remained the mainstay in the treatment and control of craniopharyngiomas. Surgical approach to craniopharyngioma has been refined further by an improved understanding of their embryology, origin, pathogenesis and pathology. The optimal surgical management of craniopharyngioma has continued to evolve, partly due to the shifting landscape brought about by an

improved understanding and knowledge of the peritumoural microanatomy. Gross total resection (GTR) has been shown to be feasible and remains the gold standard, despite a high hypothalamus-related morbidity. After the intimate anatomical relationship of the tumour with the hypothalamus, neurohypophysis and optic apparatus was made apparent, the challenge has been to remove the tumour completely without collateral damage to these vital structures. Advances in imaging, advances in skull base techniques aided by knowledge of microanatomy, and advances in HRT have made radical resection of these tumours possible with good outcomes.[30-32] Puget *et al*.,[19] in a retrospective study of two cohorts (103 and 22, respectively) defined the extent of hypothalamic involvement preoperatively so as to plan surgical treatment without damaging the hypothalamus; and, the operative risks were perceived to be minimized by preoperatively identifying the children with likely hypothalamic involvement. Aggressive or radical resection is considered in these tumours, especially in children. The outcome in craniopharyngioma treatment is evaluated in terms of mortality, visual status, endocrinal function and neurocognitive deficits, affecting the quality of life.[19,33,34]

Literature on surgery for craniopharyngioma from India is sparse, and the first authentic reports of high volume surgical intervention appeared only in 1991, in a special volume of Neurology India. The article by SNB gives an outline of the surgical and non-surgical management, a treatment plan with options depending on variables such as the size of the tumour, the cystic versus solid component of the tumour, and the size of postoperative residual tumour. Articles by Profs SN Bhagwati (SNB)[35] and AK Banerji[36] are written in the first person account, and present a review of decades of their surgical experience in tackling these tumours. Venkatramna *et al*.,[37] recorded their experience in the surgical management of 56 children with craniopharyngiomas, and recorded an overall mortality of 25%. On the other hand, Kak and Yadav[38] reported four deaths in a series of 59 craniopharyngioma patients. Rout *et al*.,[39] achieved total tumour excision in four out of 35 patients, and had four postoperative deaths. Dharker *et al*.,[40] and Deopujari *et al*.,[41] gave their consolidated experience with craniopharyngiomas in the Indian scenario. Bhagwati *et al*.,[42] published the first report of the trans-lamina terminalis approach for retrochiasmatic craniopharyngiomas.

An evolution of the cranial surgical approaches is given below, especially in the light of improved understanding of the normal and abnormal microanatomy, and pathology.

Cranial Approaches

The surgical approaches in SNB's article were based upon the direction of trajectory of approach and the extent of growth of the tumour. Most of his patients underwent excision by the unilateral subfrontal approach (37/56). A bifrontal approach, a pterional approach, a transcallosal approach and a transventricular approach were also performed in some patients based upon the patterns of tumour growth. According to the axis of extension and their growth into various compartments, Samii and Tatagiba[43] divided craniopharyngiomas into five types, while Yasargil divided them into six types. A recent classification by Morisako *et al*.,[44] gives a practical classification that classifies the tumours according to their site of origin. These tumours can thus either be intrasellar (arising within the sella), arising from anterior part of the stalk and growing into the prechiasmatic space, arising from the posterior part of the stalk and growing into retrochiasmatic space, and those located at the floor of the third ventricle being purely intraventricular craniopharyngiomas.

The rare intrasellar or intracisternal tumours located in the sub-diaphragmatic portion can be treated by a transsphenoidal approach. Tumours extending to the lower part of the third ventricle can be treated by the transcallosal or the transcortical approach. Small retrochiasmal craniopharyngiomas can be removed by the subtemporal approach. For those tumours extending to the posterior fossa, the trans-petrosal approach can be used. However, these tumours are very often of a mixed type. Craniopharyngiomas extending from the sellar–suprasellar region to the third or lateral ventricle (that confirm to type III, IV, and V of Samii's classification)[43] present a particular problem because of the risk of damage to the optic pathways and the hypothalamus. Multi-lobulated, multi-compartmental craniopharyngiomas differ from the suprasellar tumours in presentation, endocrinological manifestations and surgical morbidity.

A plethora of cranial and skull base surgical approaches have been described for tackling craniopharyngiomas. These include the anterolateral (fronto-orbital, pterional, orbito-zygomatic, supraorbital keyhole), the lateral (combined transpetrosal and temporal) and the midline (bifrontal and extended bifrontal, interhemispheric) approaches.[21] Pure intra-third ventricular tumours need to be tackled by the transcortical or the transcallosal approaches.

Anterolateral Approaches

Craniopharyngiomas can be excised by the anterolateral (unilateral) approaches, through the Sylvian fissure or the subfrontal corridor. Lateral supraorbital (keyhole) approach has also been described.[45]

Anterolateral approach

After the patient is placed in a supine position with neck slightly extended and head rotated 30 to 45 degrees to the opposite side (making malar eminence the highest point), a curvilinear incision beginning at the mid-point of zygoma is made behind the hairline. A galeocutaneous flap is raised and a frontal nerve-sparing dissection of the temporalis muscle is performed, preserving a collar of the temporalis fascia for closure. The temporalis muscle is reflected till the zygoma and the craniotomy is carried out as per the surgeon's preference, whether a pterional, a frontotemporal or an orbitozygomatic exposure. The dura is opened and after draining the cisternal cerebrospinal fluid (CSF), the Sylvian fissure is opened to visualize the optic apparatus and the tumour. A visual assessment of the tumour is carried out and correlated with the displayed imaging in the operating room. The bridging veins from the temporal lobe may have to be divided for improving the adequacy of exposure of the tumour. An arachnoid plane is identified at the most visible part of the tumour, and this is preserved as far as possible. The cystic component of the tumour is emptied of its "machine oil" contents, and the tumour wall is removed piecemeal, staying within the arachnoid plane.

The Penfield dissector number 4 and a ball-tipped dissector are quite useful in gradually loosening the tumour capsule, while the latter is gripped with a tumour forceps. Solid, calcified portions of the tumour can be crushed and removed, while the softer portions can be removed using an ultrasonic aspirator. Tumour debulking is effected through various corridors: subchiasmatic, optico-carotid and lateral to carotid. Removal of the retrochiasmatic tumour will need opening of the lamina terminalis, gradual defining of the tumour margin, and the gentle separation of the tumour with a dissector, while exerting a slight traction to open up the cleavage between the tumour and the brain.

While working through the optico-carotid and the subchiasmatic corridors, the tumour removal is satisfactorily achieved; however, removal of the retrochiasmatic and intra-third ventricular components of the tumour can be challenging.[21] Working through multiple corridors in between the nerves and arteries makes these structures and the perforators traversing through the cisterns particularly vulnerable to injury.

Supraorbital keyhole approach

This approach can be considered after a careful patient selection. The patient is positioned supine with the head extended and turned 30 degrees to the left, in the case a right-sided approach is adopted. The skin incision may be supraciliary or transciliary, lateral to the supraorbital nerve, and is centered on the key-burr hole site across the superior temporal line. The pericranium is reflected inferiorly, and the temporalis muscle is peeled off and retracted. A free bone flap of the size of 2.5 cm × 1.75 cm is made, with its lower margin being flush with the orbital roof. The surgeon may wish to include the supraorbital ridge in the bone flap. The dura is opened and reflected caudally, and the frontal pole is gently lifted to suck out the CSF from the suprasellar cisterns. A thin malleable retractor is advanced until the optic foramen, and the cisterns are further opened. The Sylvian cistern is opened and adequate brain relaxation is achieved. The tumour is defined and decompressed under an operating microscope [Figure 3]. The microscope needs to be frequently moved to visualize all aspects of the anatomy and the tumour extension, while working through the subchiasmatic and the optico-carotid corridors, between the optic nerves, under the chiasm, and around the optic nerves and the internal carotid artery (ICA).

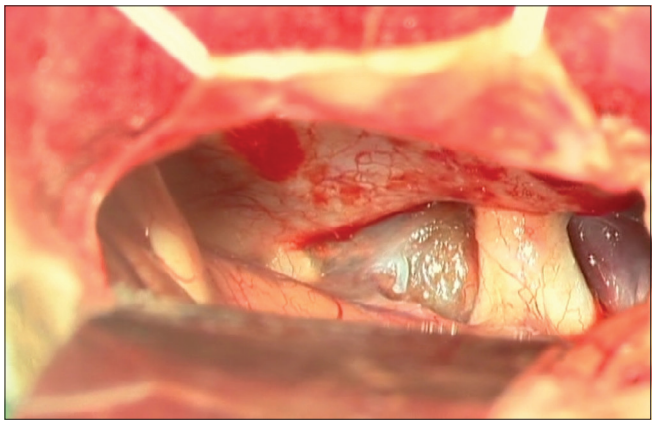

Figure 3: Intraoperative view showing the craniopharyngioma as seen by the supraorbital keyhole exposure

Part of the tumour under the ipsilateral optic nerve and the ICA may be difficult to visualize, and an endoscope may be useful for this purpose. Although small sellar, suprasuprasellar tumours can be removed successfully utilizing this approach,[46] this approach may be found deficient for retrosellar and intra-third ventricular tumours.

Tackling intra-third ventricular tumours

Pure intra-third ventricular craniopharyngiomas are rare. Reviewed extensively by Pascual *et al.*,[47] these tumours may either be of the adamantinomatous or the papillary types in equal numbers and proportion. A rare combination of a pure intra-third ventricular craniopharyngioma and growth hormone-secreting pituitary adenoma has been reported.[48] These tumours are best excised by the transcranial route, either by the transcallosal approach, or by transcortical-transventricular approach and foraminal entry through the foramen of Monro [Figure 4A and B].

Bifrontal craniotomy

Six of SNB's patients underwent tumour excision by the bifrontal approach. Large, multilobulated, partly cystic and variably calcified craniopharyngiomas need to be addressed from multiple angles, often changing the angle, magnification and depth of the operating microscope. A midline tumour with bilateral multi-compartmental extension including the retrochiasmatic and retroinfundibular extensions, can be perfectly tackled by the bifrontal approach.[25,49,50] The approach, a combination of the frontal interhemispheric and the trans-lamina terminalis approaches gives an excellent view of the entire anatomy and pathology of the region [Figure 5A].[51] Retraction to the frontal lobe(s) is minimal, and once the tumour is exposed, the decision to do away with the retractors can be taken. The bifrontal craniotomy is unique in its ability to provide the kind of exposure no other approach does, and reconstruction or craniotomy closure is fairly simple, unlike some of the other anterior skull base procedures. Due to the neck extension, there is little retraction required as the frontal lobes undergo a gravity-dependent retraction of the frontal lobe from the skull base. The cranial nerves I – III, the optic chiasma and the pituitary stalk can be preserved and displayed. A lateral approach, more often than not, necessitates sacrifice of the ipsilateral olfactory tract, by design or following its avulsion

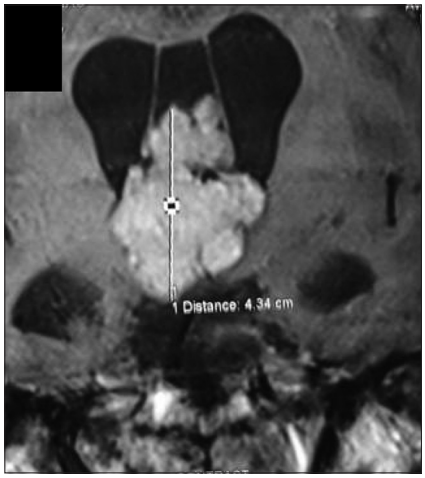

Figure 4A: Patient 3: Intra-third ventricular craniopharyngioma

due to frontal lobe retraction. The bifrontal craniotomy gives a panoramic view of the entire anterior cranial fossa, sellar, suprasellar and parasellar regions, the lamina terminalis, and most importantly, a view of the abnormal anatomy of the arachnoid covering the tumour and the perforators in its vicinity [Figure 5B]. Multiple arachnoid cisterns can be opened for achieving a lax brain and for removal of the tumour from various compartments. The most obvious advantage is the preservation of the normal orientation of the anatomy. A unilateral frontal or a lateral approach to the tumour, however, requires a special orientation of the anatomy. The ability to reach the lamina terminalis directly in the midline is a major advantage [Figure 6A-C]. Moreover, the midline approach affords easier identification of pituitary stalk.[52] In SNB's series, the lamina terminalis was opened in eight patients.

Endoscopic endonasal transsphenoidal approach

The minimally invasive endoscopic approaches have revolutionised surgery for craniopharyngiomas as they provide an 'incisionless direct access' to the tumour.[53-55] In this surgery, the patient is positioned supine on the operating table with the head either placed on a horse-shoe head rest or fixed in a head holder. The head is flexed toward the left shoulder by 15°-20^0, and rotated by 15° to the right side. In the endonasal 'uninostril' method, the mucosal layer overlying the bony part of the vomer is incised after entering through the anterior nares into the nasal cavity. The mucosa over the body of the vomer is gently separated until the rostrum of the sphenoid and the sphenoidal ostia are visible. The bony vomer is gently fractured and retracted to the opposite side, thus gaining access bilaterally to the rostum and ostia of the sphenoid without opening the mucosal layer of the opposite nasal cavity.

In the 'binostril, bimanual' technique, both nasal cavities are used for surgery, with the endoscope placed in the upper half of one nostril by one surgeon, and the other surgeon using the lower half of the same nostril for suction, and the entire opposite nasal cavity for passing instruments for tumour dissection. The middle turbinate is retracted laterally, and initially, a nasoseptal flap is created. Then, traversing along the medial surface of the superior turbinate, the sphenoidal ostia is identified and enlarged. A posterior septectomy is created by excising the vomer and the perpendicular plate of ethmoid, followed by resection of the sphenoid rostrum. A wide sphenoidotomy is done, which is followed by removal of bony septations and mucosa within the sphenoid sinus.

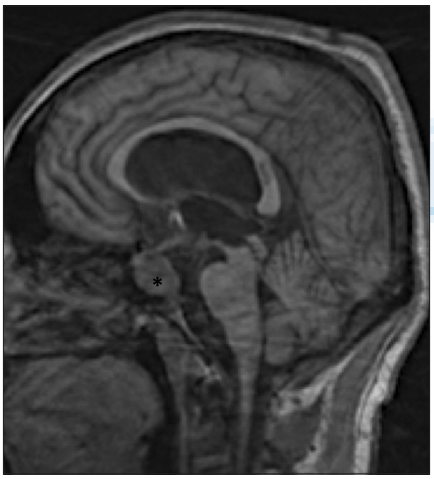

Figure 4B: Postoperative T1-weighted contrast MRI showing tumour excision

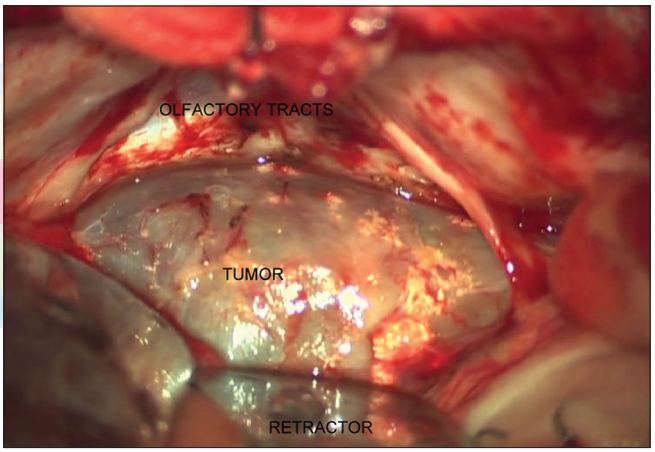

Figure 5A: Bifrontal craniotomy showing a cystic craniopharyngioma and splaying of olfactory tracts

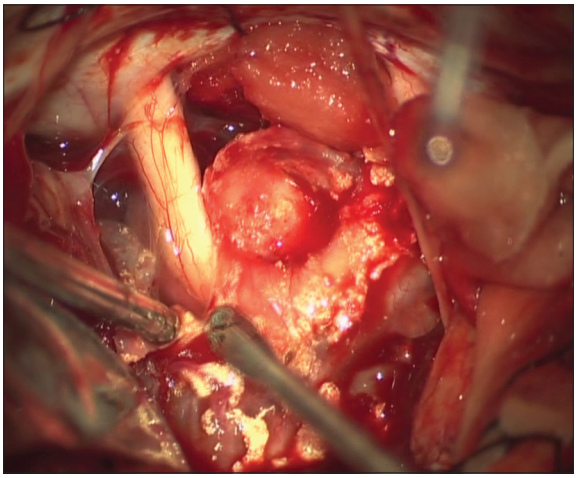

Figure 5B: Dissection of craniopharyngioma off the optic apparatus

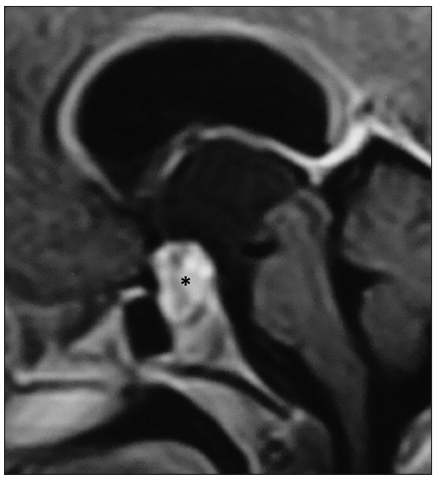

Figure 6A: Patient 4: Sagittal contrast T1 weighted MRI showing a cystic and solid retrochiasmatic tumour (*)

The sella is identified between the carotid prominences on both the sides, and the clival recess is visible inferior to the sella. In case a subfrontal exposure is also required, removal of bone of the tuberculum sellae, planum sphenoidale and medial opticocarotid recess widens the intradural exposure and provides an early identification of the optic nerves and the internal carotid artery. The sellar floor is either drilled out using a drill or removed using a Kerrison's punch. The sellar dura is identified between the dura covering the cavernous sinuses on both the sides laterally, and the superior and inferior intercavernous sinuses in the midline. Opened the dura exposes the intrasellar tumour. If needed, an anterior dural opening along the planum sphenoidale may be undertaken to access the craniopharyngioma along the anterior skull base. Extensive bone removal from the sellar floor along the inferior intercavernous sinus, and sometimes the posterior clinoid processes and dorsum sellae, may be required to expose the retroinfundibular craniopharyngiomas extending from the infundibulum into the prepontine and interpeduncular cisterns. Piecemeal tumour removal is performed. The thin arachnoidal layer of the suprasellar cistern over the tumour should be opened sharply, and a plane of dissection between the overlying arachnoid and the tumour capsule must be identified. The Liliequist membrane is intact and serves as a protective barrier for the brainstem, basilar artery and posterior cerebral arteries. Closure may be performed by placing autologous fat grafts in the sella and sphenoid sinus with a fascial graft overlay. In the endonasal 'uninostril' method, the laterally displaced mucosa is displaced back to its original position medially and approximated to the vomer and the mucosa of the opposite side. In the 'binostril' technique, the vascularized pedicled, nasoseptal flap is rotated to cover the cavity filled with the fat graft and held in place by administration of fibrin glue. In the cases, where an suprasellar tumour removal has been performed after opening the suprasellar arachnoidal layer, CSF drainage using a lumbar catheter may continued for 5 postoperative days [Figure 7A-E].[56]

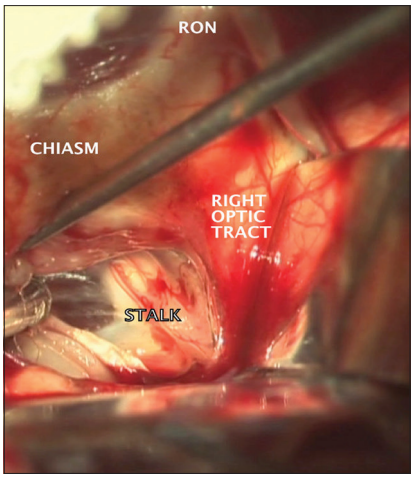

Figure 6B: Pituitary stalk seen after excision of tumour through lamina terminalis

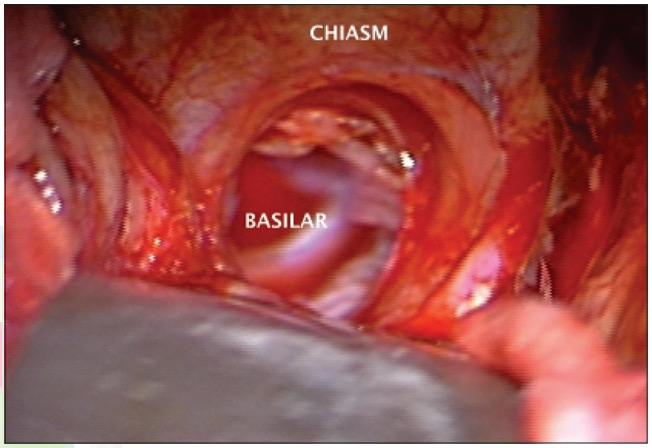

Figure 6C: Basilar top seen after excision of tumour through lamina terminalis

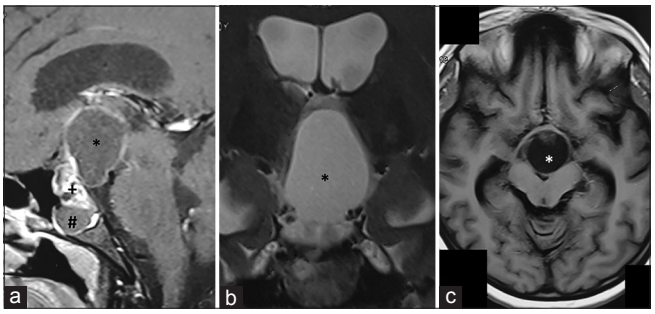

Figure 7A: Patient 5: (a) Contrast enhanced sagittal T1 weighted image showing a tumor extending from third ventricle (*) to the sellar-suprasellar region (+) and the sphenoid sinus (#); (b) T2 weighted coronal image showing the intra-third ventricular cystic component of the tumor; and (c) T1 weighted contrast enhanced axial images showing the cystic tumor splaying the cerebral peduncles

Alternative or Adjunctive Therapies

Due to the postoperative morbidity, there was a trend towards conservative excision of these tumours, often restricted to cyst aspiration. This was followed up with radiation therapy and intracavitory instillation of radioactive isotopes, interferon and bleomycin. Since the 1970s, less aggressive surgery coupled with irradiation has been shown to be effective.[28,34,57,58] Irradiation may not be the perfect solution considering the long-term sequelae as well as the high recurrence rates, radiation induced changes and neurological morbidity. Attempts to limit the damage by partial excision or biopsy and cyst evacuation, followed by radiotherapy have the flip side of radiation induced injury to the brain, especially in the children, and the occurrence of neurocognitive deficits.

Irradiation

Surgery offers the best chance for complete tumour excision, although this may not be achieved due to various factors. Incomplete tumour excision (partial, subtotal or biopsy only) will necessitate irradiation of these otherwise benign tumours, so that their growth is arrested and neuroendocrinological complications are avoided. Radiotherapy (RT) is also effective in the setting of recurrent disease. Four children in SNB's series were subjected to irradiation, after their tumour had recurred. Radiation therapy (RT) was repeated in one child after a second recurrence, five years after the first therapy had been administered. Eleven of the thirteen adults who had a residual tumour after their first surgery were irradiated. The local control rate following RT varies between 84 to 86%.[28,58] There does not appear to be a dose-response relationship, and high control rates have been achieved with doses of 5400 to 5580 cGy.[28] The tumour volume

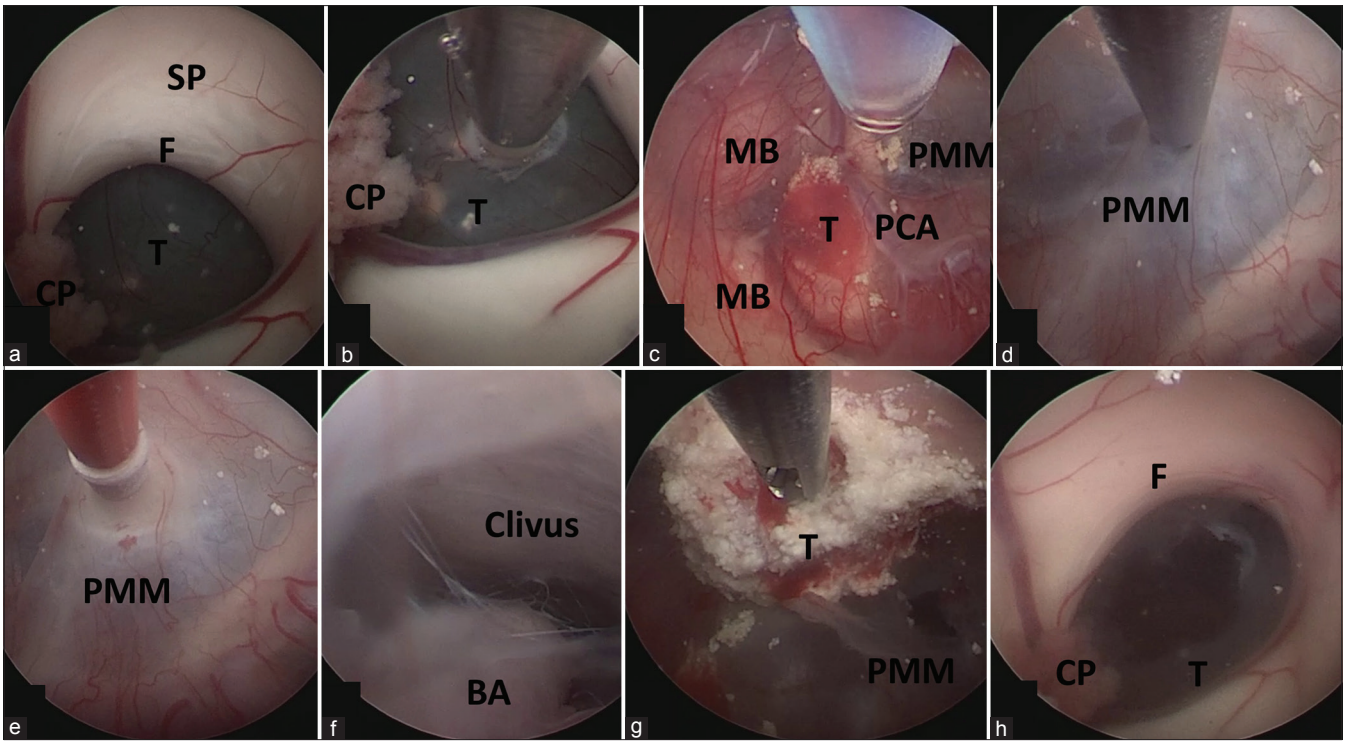

Figure 7B: The initial endoscopic transcortical, transventricular, transforaminal approach with fenestration of the wall of the tumor at foramen of Monro as well as at the floor of the third ventricle with biopsy of solid tumor along the third ventricular wall; (a) The tumor wall (T) seen at the foramen of Monro stretching the fornix (F) and causing bulging of the septum pellucidum (SP); The choroid plexus (CP) is also seen; (b) The tumor wall (T) is fenestrated using monopolar cautery; (c) At the floor of the third ventricle, both the mammillary bodies are seen. The tumor (T) is occupying the suprasellar space and the basilar apex and the posterior cerebral arteries (PCA) are seen through the thin floor of the third ventricle at the premamillary membrane (PMM); (d) The premamillary membrane (PMM) is opened using a biopsy forceps; (e) The fenestration created is enlarged using a 4F Fogarty's balloon catheter; (f) The interpeduncular and prepontine space posterior to the clivus is entered and the basilar artery (BA) visualised; (g) The endoscope is withdrawn into the third ventricle showing the premamillary membrane (PMM) breach and the calcified tumor (T) along the lateral wall from which biopsy is taken; and (h) The endscope is withdrawn into the third ventricle showing the fenestration in the tumor capsule (T) at the foramen of Monro. The fornix (F) and choroid plexus (CP) are also seen

that needs to be included in the RT protocol is defined as the tumour with a margin of 5–10 mm, and should include the cystic component of the tumour also. The tumour delineation must be accurately performed to avoid damage to the hypothalamus and the optic apparatus. A major concern is the expansion of the cyst during and after radiation therapy. In a study on 27 patients of craniopharyngiomas undergoing postoperative intensity modulated radiation therapy (IMRT), Lamiman *et al.*,[59] observed the occurrence of cyst expansion in 40% of the patients. They contended, however, that the cyst expansion is generally a self-limiting process without any untoward side-effects. If the cyst expansion causes progressive hydrocephalus, it may be treated with a ventriculoperitoneal shunt. For patients with a solitary cyst expansion, cyst aspiration and/or administration of intracystic interferon may result in disease control.

The techniques of RT are:

Conformal irradiation

Until the seventies, conformal RT was given with cobalt-60. Later, it was changed to linear accelerator allowing 'arc rotation', so that the dose to the surrounding brain could be decreased. Improved tumour delineation by the MRI has enable the administration of three dimensional (3D) conformal irradiation. This technique has significantly improved the definition of tumour volumes.[60]

Stereotactic radiosurgery (SRS)

SRS involves the delivery of single fraction of radiation with a non-relocatable head frame, utilizing the MRI-guided planning. It allows for a sub-millimeter accuracy with sparing of surrounding vital structures. In craniopharyngiomas, however, the target tissue should be smaller than 3 cm, and the optic apparatus can tolerate only 800 cGy in a single fraction. Vital structures should be at least 3 mm away from the radiation field. Kobayashi *et al.*,[61] reported the treatment outcomes of 107 craniopharyngioma patients (of these included patients, 38 patients were less than 15 years in age) treated with gamma knife. The prescribed dose was 11.5 Gy. With a median follow up of 65.5 months, the control rate was 79.6% and the complete response rate was 19.4%. The 10-year survival rates were 91%. A dose of 12 Gy may be adequate for tumour control,[61,62] and the dose to the optic apparatus in the vicinity should not exceed 8 Gy. A highly conformal plan should be tailored to minimize dosing to the optic apparatus, using smaller radiation doses. Cystic enlargement of craniopharyngiomas can occur after gamma knife surgery, leading to visual deterioration,[63] which may require aspiration of the cyst for immediate relief.

Fractionated stereotactic radiotherapy (FSRT)

Tumours close to the optic apparatus can be treated by fractionation of the radiation dose. It requires immobilization

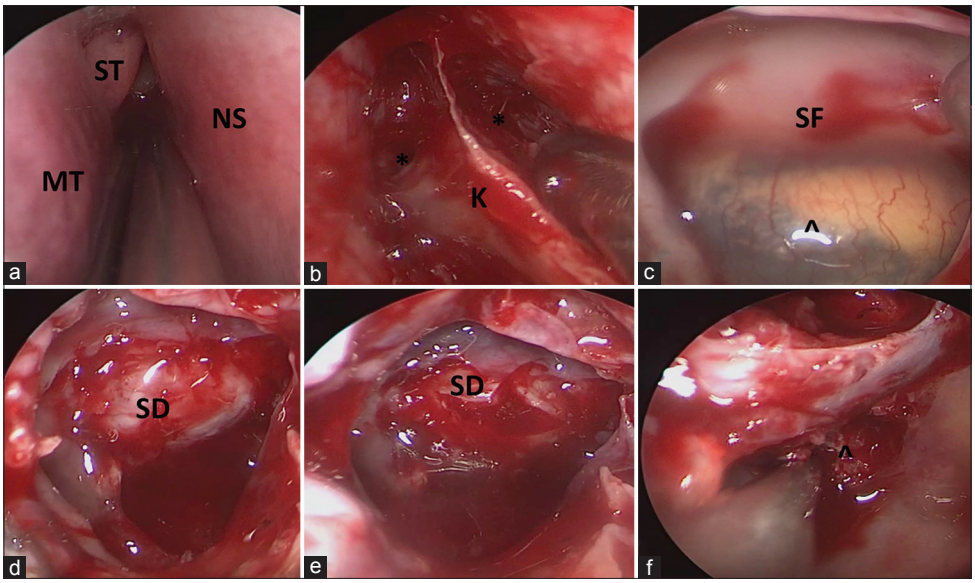

Figure 7C: Under the same anaesthesia, an endoscopic transnasal uninostril approach is also performed. (a) Traversing the endoscope along the medial aspect of the middle turbinate (MT), the region between the superior turbinate (ST) and the midline nasal septum (NS) is enlarged; (b) The mucosa over the bony part of the nasal septum is elevated to reach the rostrum of the sphenoid sinus (R) and the sphenoidal ostia (*); (c) The bony floor of the sella covered by mucosa as well the sphenoidal part of the tumor in the sphenoclival recess are seen; (d) The sellar floor is removed exposing the sellar dura; (e) The sphenoidal part of the tumor is addressed by removing the cystic component of the tumor; (f) The sphenoidal solid part of the tumor is also removed

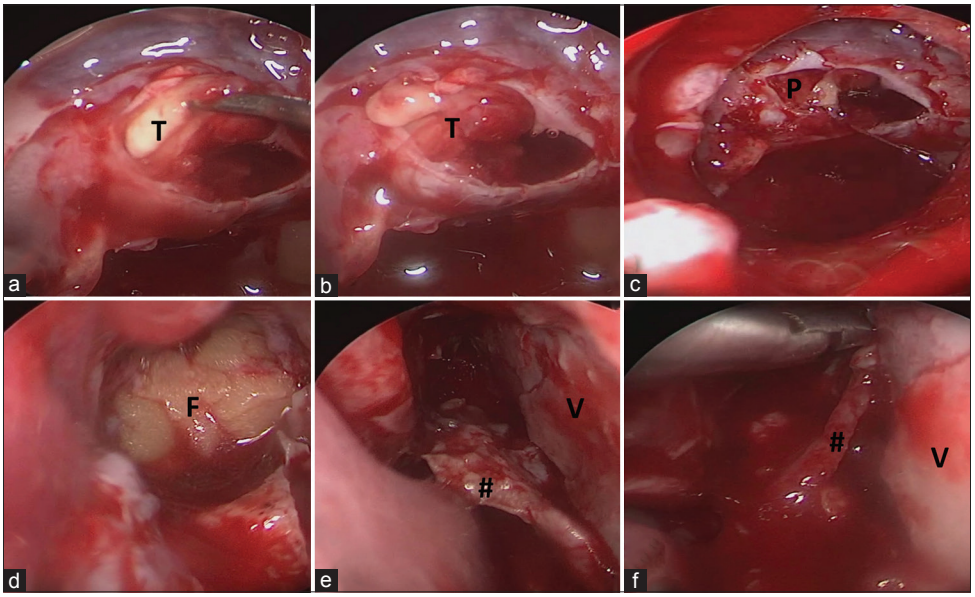

Figure 7D: Continuing the endoscopic transnasal uninostril approach, (a) The sellar part of the tumor (T) is dissected using ring curettes; (b) The tumor (T) is exposed in the sella and removed using biopsy forceps; (c) After tumor removal, the normal pituitary gland (P) is visualised; (d) The sellar and sphenoidal cavity is packed with autologous fat (F) harvested form the peri-umbilical area; (e and f) The ipsilateral nasal mucosa (#) is replaced over the vomer firmly obliterating the operative trajectory and held in place by fibrin glue. An intrathecal lumbar drainage was also placed to prevent CSF leak

with a rigid relocatable frame and daily administration of the calculated dose. A recent series has reported 100% control with FSRT with a median dose of 5220 cGy.[64]

Late effects of irradiation

Radiation to the paediatric brain may cause undesirable and damaging sequelae. Endocrinopathies, optic neuropathy, neurocognitive deficits, radionecrosis, vascular injury leading to moya moya disease are prominent morbidities seen after cranial radiation.

The evolution and availability of computer guided stereotactic therapies have established the non-surgical modalities as viable options and add-ons that reduce and avoid the morbidity of the surgical procedures.

Intracavitary Therapy

A cystic cavity may often be the main component of craniopharyngiomas, which can be exploited for institution of therapy and for control of the tumour. The liquid contents of

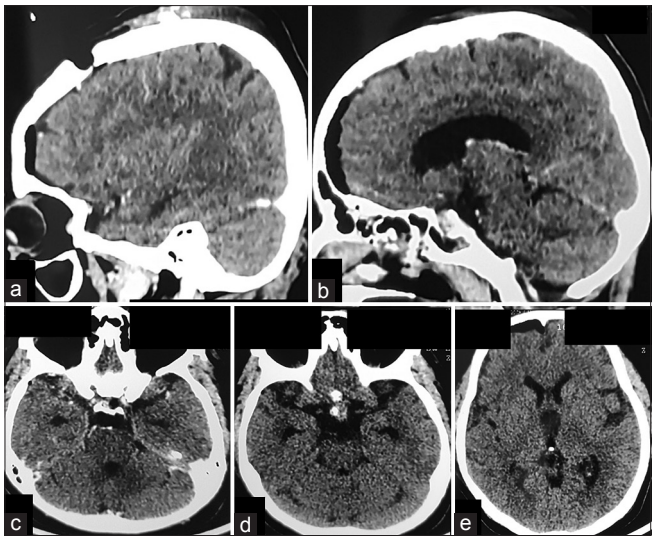

Figure 7E: The contrast enhanced (a-b) Sagittal reconstructed images of CT scan; and (c-e) Axial images showing a small residual tumor at the floor of the third ventricle

the cyst in the adamantinomatous type of craniophrayngiomas appear oily, and are rich in cholesterol, keratin and occasionally calcium. The cyst fluid of the papillary craniopharyngiomas is less oily and appears less dark, with absence of calcification. Distension of the cyst due to its liquid contents adds to the tumour bulk and increases the pressure on the surrounding structures; and, decompression provides an immediate relief.

Aspiration

The first definite documented aspiration of cystic craniopharyngioma is attributed to Kanavel,[65] who aspirated the cyst by the transsphenoidal route, to relieve the patient of the headache and the visual symptoms. Kanavel repeated the aspiration twice, two months later, and at the time of aspiration six months later, he took a biopsy of the cyst wall. The histopathology revealed a cystic tumour composed of stratified squamous epithelium. Stereotactic aspiration today at best is a palliative measure, while awaiting the effects of intracavitatory irradiation. Repeated aspiration tends to stimulate fluid production, leading to shortened symptom-free intervals.[60] Solid tumour growth, however, continues unimpeded and may extend into the emptied cysts. Hence, a simple stereotactic aspiration of the tumour cysts or placement of an Ommaya reservoir into the cyst for serial aspirations is never indicated as a primary therapy.

Intracavitary irradiation

This was an effort to preserve the visual, limbic and hypothalamic functions by neutralizing the tumour wall with agents that irradiate the cyst wall and have a rapid fall-off that avoids collateral damage to the normal neural structures. Whereas only 10% of craniopharyngiomas are solid, the great majority have a cystic component which can be addressed with endocavitory irradiation with a ß-emitter (^{186}Re, ^{32}P, ^{198}Au, ^{90}Y).[66] The two isotopes that have been extensively used are Yttirium-90 and Phosphorus-32, with an ideal dosage of 200-250 Gy to the cyst wall.[67-69] A radioisotope of phosphorus (^{32}P) is used preferentially due to its enhanced half-life and shorter penetration beyond the cyst wall. The isotope is inserted stereotactically. Cyst regression occurs over several months and diminution or obliteration of the cyst is seen in 74 to 100% of the cases.[68-72] A durable control is seen in 80 to 96% of the patients,[68,71] and cyst shrinkage occurs over 3 – 18 months.[68] The treatment related mortality is low, and the principal morbidity appears to be optic atrophy.[71,72] A relatively recent report pertaining to the instillation of colloidal^{186}Re (Rhenium) in 54 patients reported complete or partial cyst resolution in 70% of the patients with improvement in the visual symptoms in 12 patients, and improved cognitive status in 10 out of 17 (those with preoperative cognitive impairment) patients.[66] New onset endocrinal, neurological or cognitive decline is rare. Intracystic irradiation can often be combined with stereotactic radiosurgery in patients with a smaller solid and a larger cystic component.

Intracavitary bleomycin

Bleomycin, an antineoplastic antibiotic that interferes with deoxyribose nucleic acid (DNA) metabolism, can be injected within the tumour cavity through an Ommaya reservoir at a 1-2 day interval in the dose of 1.5 to 10 mg over a two to three week period, the average total dose being 60 to 80 mg. Involution of the cyst occurs slowly over several months, with half of the patients being treated showing complete disappearance of the cyst.[73] The cyst wall becomes tough and fibrous, though it does not disturb arachnoidal planes. Hence, post-instillation of bleomycin, the tumour wall is easier to grip and dissect as compared with the thin diaphanous wall of an untreated tumour. Delayed complications include peritumoural edema, hypothalamic dysfunction, seizure and vasculopathy.[74,75]

Intracavitary interferon

Interferon alpha has been used as both systemic and intracavitary therapy for primary craniopharyngiomas in recent studies. Cavalheiro and colleagues[76] have reported a trial of intracavitary interferon alpha in 60 children. A short-term disease control (greater than 50% decrease in the tumour volume) was seen in 78% of the patients; 13% had new endocrine deficiencies and 30% had mild side effects. Interestingly, three of the responders had previously experienced tumour progression after bleomycin but were salvaged with interferon. Long-term sequelae and outcome of this therapy are not known.

Recurrent Craniopharyngioma

Leaving a residue of the tumour behind in an effort to prevent neurological deterioration goes hand-in-hand with the risk of recurrence. Seemingly gross total resection too is not an assurance against recurrence of the tumour. In SNB's article, 17 patients underwent total resection, and seven had a recurrence. One child underwent a craniotomy four times for his tumour recurrence. Postoperative irradiation can arrest further tumour growth in patients who have undergone a subtotal excision. However, recurrence occurred in SNB's series in about half of the patients who underwent irradiation, in the form of cyst formation and increase in the size of tumour, necessitating a repeat craniotomy. One child was subjected to a repeat cobalt therapy.

The single consistent factor associated with recurrence is the extent of resection at the initial surgery.[77] Other factors are a

large tumour size (>5 cm), an extensive calcification, and an extensive suprasellar extension.[17,77,78] Lower recurrence rates are noticed when postoperative irradiation is used, irrespective of performance of an initial gross total resection or a lesser procedure.[79]

Management of recurrent craniopharyngiomas is challenging and peppered with controversies. There is paucity of consensus since the treatment is highly individualized and tailor-made for a a particular patient-related situation. The management of a recurrent tumour needs a team comprising a neurosurgeon, endocrinologist, radiation oncologist, pediatric neurologist and a psychologist. The family of the patient should participate in the decision-making process, so that they can be supportive in the event of development of side effects of therapy and occurrence of fresh neurological deficits. The treatment depends on a number of factors, such as the extent of previous surgery, the neurological status of the patient and the specific neurological deficits, the size of recurrence, the type of recurrence (cystic versus solid), the extent of involvement of brain (hypothalamus, optic apparatus and cerebrum), the presence of hydrocephalus and cognitive impairment. Options for treatment in the presence of a recurrent tumour include a reoperation, intracystic therapy with bleomycin or beta-emitting isotopes, fractionated radiotherapy, stereotactic radiosurgery, or some combination thereof. There may be further need for repeated cyst aspiration and CSF shunting.

Some New Concepts

Hormonal expression status and its impact on hormonal replacement in residual tumours

Hormonal receptor expressivity has been shown for growth hormone (insulin-like growth factor [IGF]-1 receptor expression), estrogen and progesterone receptor expression, and abundant expression of obesity (Ob-RA6.4 and Ob-RA12.1) receptors.[80] Whether the assessment of receptor status and administration of hormones in the form of hormonal replacement therapy, or the evaluation of Ki-67 and CD34 labelling index is a predictive factor for tumour recurrence and enlargement requires further studies.[81]

Application of molecular pathology to therapy

Clinically and on imaging, craniopharyngioma appears as a heterogenous disease. Some tumours, both cystic or solid, may remain indolent for years despite the presence of residual tumour, with or without radiotherapy; while others follow an aggressive course with a rapid recurrence despite all forms of therapy.[82] Molecular pathology and study of genetic expression is under evolution. Although there are no clear-cut therapeutic translation modules available, this is a field to watch.[83] High mutation rates of v-raf murine sarcoma viral oncogene homolog B1 (BRAF V600E) in papillary craniopharyngioma and of CTNNB1 (beta catenin) in adamantinomatous craniopharyngioma have been shown.[84] These activating driver mutations are potential therapeutic targets. Significant response to BRAF/MEK (mitogen-activated protein kinase) inhibition in a patient with multiple recurrent papillary craniopharyngioma has been reported.[84] These targetable mutations warrant prospective research, and in the background of genomic discovery, the treatment paradigm of craniopharyngioma is likely to change.

Malignant Change

SNB's article does not mention any instance of malignant change in a pre-existing craniopharyngioma. Progression to malignancy is extremely rare, and is limited to the adamantinomatous variant.[85,86] Rodriguez *et al*.,[85] did a literature review and found eight instances of squamous cell carcinoma supervening in operated patients with an adamantinomatous craniopharyngioma, all of whom had undergone prior radiation therapy. They added three patients, all of whom were diagnosed as malignant craniopharyngioma (in contrast to squamous cell carcinoma), and two of those had received prior radiation. An interesting finding in in these three specimens were p53 expressivity, along with a high MIB1 index. All the patients reported in the literature review as well as those reported by the authors were dead within six months. It is concluded that malignant change in craniopharyngiomas is extremely rare, generally occurring after multiple recurrences, and has a uniformly fatal outcome.

Evolution of Management

Since the publication of SNB's article, and the compilation of data on craniopharyngiomas from India in 1991, the management of craniopharyngiomas has evolved. Pioneering efforts of Drs. SNB, Banerji, Deopujari, Rout and Kak have resulted in a gradual reduction in the operative mortality.[35-42,87] Following surgery, hormone replacement therapy and a close monitoring of the endocrinological status as well as quality of life (QOL) issues require addressal. The compromise of visual function, the occurrence of hypothalamic obesity and the effects of the tumour as well as its management on cognition, learning and scholastic performance remain the prevalent challenges. Tumour recurrence, whenever it occurs, remains a major setback to the QOL of the patient as well as the therapeutic protocols. Surgery remains the single most effective therapeutic measure, and that needs a firm commitment from the surgeon.

Outcomes in craniopharyngioma surgery have served as a benchmark for pediatric neurosurgery. In view of the high morbidity and hypothalamic damage, therapeutic protocols with less invasive approaches (partial excision, cyst aspiration) followed by irradiation have been worked out. However, damage to the growing brain by radiation and repeated surgery continued to project a life with severe hypothalamic and visual morbidities, and learning disabilities. With better understanding of the sellar and suprasellar microanatomy, as well as better postoperative critical care monitoring and hormone replacement therapy, a renewed look is being given to radical excision of these tumours. Lindholm and Nielsen[82] echo the present sentiment quite succinctly:

"*Though this tumour is still an ominous disease, it seems fair to say that the outlook has improved considerably*."

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Conflicts of interest
There are no conflicts of interest.

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FROM THE TREASURE TROVE OF NEUROLOGY INDIA

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CRANIOPHARYNGIOMA

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Craniopharyngioma offers the most baffling problem which confronts the neurosurgeon. It has always proved a challenging and a frustrating tumour to the neurological surgeons, because, despite its benign nature, histologically, there have been almost insurmountable technical and physiological difficulties incident to its surgical manipulation.

Harvey Cushing, 1925

Surgical manipulation of craniopharyngioma has been considered to be a challenge from the time of Cushing, as its complete removal is attendant with a high risk of morbidity and mortality due to its adherence to the surrounding vital structures (Manaka *et al*. 1985). This has been so despite development of better operating facilities, improved anaesthesia and greater understanding of postoperative physiological and endocrinological disturbances, especially when the tumour is large and retrochiasmal in location (Patterson and Danylwich 1980).

Therefore, a fair amount of controversy continues to surround the issue of management of craniopharyngioma, whether it be radical removal, partial removal, radiotherapy or a combination of these modalities (Hoffmann 1982). A total removal of the tumour would be an ideal form of treatment as partial removal tends to result in its recurrence. This is feasible when the tumour is small and not adherent to the hypothalamus or the optic pathways. It may be better to excise it partially or subtotally if it is not possible to excise it safely, leaving the person neurologically intact and functionally normal. Does palliative surgery to relieve pressure on the optic pathways or to relieve hydrocephalus in such cases postpone the inevitable only for a while? Or when combined with radiotherapy, does it help to achieve a long-term cure? How effective is radiation in arresting the further growth of these craniopharyngiomas? Are we justified in subjecting an immature or growing brain to hazards of radiation? Do patients who have had a "so called" total excision ever experience a recurrence? If so, how should they be treated? Does radiation render a reoperation more difficult? Is it possible to excise such a recurrence completely? Analysis of 56 cases of craniopharyngiomas personally treated at the Bombay Hospital was undertaken with a view to answer some of these questions.

Material and Methods

A study of 56 cases of craniopharyngiomas treated at the Bombay Hospital from 1972 to 1989 was undertaken with a minimum follow up of 1 year and maximum follow up of 17 years.

There were 37 children and 19 adults. The maximum incidence was in the first two decades, the youngest being one and half years, and the oldest 62 years of age. Amongst children, the maximum incidence was between 6 and 15 years of age.

In children, there was male preponderance, with the incidence being equal amongst males and females in adults.

Delay between the first symptoms and diagnosis was more than 6 months in nearly half the patients. Only 7 patients presented with symptoms for less than one month suggesting a fair amount of delay in diagnosis of this tumour inspite of its classic clinical features especially in childhood (Table II).

Clinical Manifestations (Table III)

Common clinical manifestations were headache, vomiting and impaired vision.

Endocrinologically, 11 patients had stunted growth, 3 had obesity, 6 had diabetes insipidus, 2 had sexual infantilism, whereas 1 had oligomenorrhea and primary sterility. Two had hypothyroidism.

Quite a few patients had unusual manifestations. Eight had generalized seizures, 1 had monoparesis, 1 had hemiparesis with sensory deficit, 1 had anosmia whereas 2 had drowsiness, disorientation and impaired memory as the presenting feature probably from associated hydrocephalus.

Visual Manifestations (Table IV)

Visual acuity was moderately impaired in 16 cases, and markedly reduced in 11 patients. There was unilateral visual loss in 7 and bilateral in 4 patients. Vision was probably unaffected in 18 patients, 13 of whom were children in whom minor changes could not be appreciated.

Seven patients had unitemporal hemianopia whereas 20 had bitemporal hemianopia. Incomplete field cutouts were difficult to assess in younger children.

Seventeen patients had papilloedema, 32 had primary optic atrophy, whereas 7 did not show any fundal changes.

TABLE I

Age group years	Number of cases
0-10	21
11-20	20
21-30	3
31-40	5
41-50	4
51-60	2
61-70	1

Youngest 1½ years, oldest 62 years

TABLE II
DELAY BETWEEN FIRST SYMPTOM AND DIAGNOSIS

<1 month	7
1-3 months	14
3-6 months	6
6-12 months	12
1-2 years	7
2-5 years	5
>5 years	5

TABLE III
CLINICAL MANIFESTATIONS

Common neurological manifestations	Number of patients	Endocrinological manifestations	Number of patients	Uncommon manifestations	Number of patients
Headache	41	Stunted growth	11	Convulsions	8
Vomiting	37	Obesity	3	Giddiness	2
Impaired vision	34	Oligomenorrhea	1	Impaired memory	2
Diplopia	1	Hypothyroidism	2	Monoparesis	1
Ptosis	1	Diabetes insipidus	6	Hemiparesis	1
		Primary sterility	1	Drowsiness	1
		Sexual infantilism	2	Disorientation	1
				Anosmia	1

Many patients had more than one clinical features at presentation

TABLE IV
VISUAL SIGNS AND SYMPTOMS

Visual acuity	Number of patients	visual fields	Number of patients	Fundal changes	Number of patients	Impaired ext. ocular movements	Number of patients
Unaffected	18	Bitemporal hemianopia	20	Normal	7	VI N paresis	
Moderate impairment		Unitemporal hemianopia	7	Papilloedema	17	Unilateral	3
Unilateral	4			Optic atrophy	32	Bilateral	2
Bilateral	12					Internal rectus paresis	1
Marked impairment						Bilateral ptosis	1
Unilateral	3						
Bilateral	8						
Loss of vision							
Unilateral	7						
Bilateral	4						

TABLE VA
RADIOLOGICAL FEATURES

X-ray skull (28)	
Calcification	19
Ballooned sella	16
Decalcification	5
Sutural separation	12
Normal	6

Calcification in 83.3% of children 40% of adults

TABLE VB
OTHER IMAGING MODALITIES

PEG	13
Ventriculography	9
Angiography	1
Nuclear scan	1
CT scan	34

PEG=Pneumoencephalography, CT=Computed tomographic

TABLE VI
SIZE OF CRANIOPHARYNGIOMA

Small (<1.5 cm)	-
Medium (1.5-3 cm)	3
Large (3-5 cm)	39
Giant (>5 cm)	14

TABLE VII
NATURE OF LESION

Cystic	18
Solid	9
Mixed	29

TABLE VIII
TYPE OF SURGERY

Lesion	Total excision	Subtotal excision	Aspiration	
Cystic	8	8	1	17
Solid	3	6	-	9
Mixed	12	17	-	29
Total	23	31	1	55

Unilateral sixth nerve paresis was present in 3 patients, bilateral in 1 patient. One patient had bilateral ptosis whereas 1 had only internal rectus paresis.

TABLE IX
CEREBROSPINAL FLUID DIVERSION

Preoperative shunt	
VA	2
Bilateral	3
Postoperative shunt	
VA	3
Unilateral VP	1
Bilateral VP	1
Preoperative external ventric drain	1
Postoperative external ventric drain	2

TABLE XA
SURGICAL APPROACH

Subfrontal	
Unilateral	37
Bilateral	6
Pterional	3
Transcallosal	2
Transventricular	3
Subtemporal	2

TABLE XB
SURGICAL APPROACH FOR PREFIXED CHIASMA 12 CASES

Lamina terminalis approach	8
Optico-carotid approach	4

TABLE XI
NUMBER OF OPERATIONS

Total excision		Subtotal excision
14	Single procedure	23
2	Two craniotomies	1
1	Three craniotomies	-
1	Four craniotomies	-
4	Craniotomy + shunt	5
1	Craniotomy + reservoir	1

TABLE XII
RESULTS OF TOTAL EXCISION

	Adults 6 cases
Postop death (hypothalamic disturbance)	1
No recurrence*	5

*1 at 1 ½ years, 3 at 3 years, 1 at 7 years (follow up)

Imaging (Table VA)

Plain X-rays of skull showed calcification in the sellar and/or suprasellar region in 19, ballooned sella in 16, and decalcification of sella in 5 patients. Sutural separation was present in 12 children. Calcification was present in 83.3% of children and 40.0% of adults.

In the pre-CT scan era, 22 patients had either pneumoencephalography or ventriculography prior to definitive surgery. CT scan was the main imaging modality in 34 of our patients (Table VB)

Size and Nature of the Lesion (Table VI)

Craniopharyngioma was designated as small when it was less than 1.5 cm in size, medium when between 1.5 – 3.0 cm, large when more than 3.0 cm, and giant when more than 5.0 cm in size or if it had grown beyond the sellar and suprasellar region into various cranial compartmental compartments.

TABLE XIIB
RESULTS OF TOTAL EXCISION

	Children (17 cases)
Postop death after surgery for 3 recurrences	1
Delayed death (second surgery elsewhere)	1
No follow up	1
No recurrence*	8
Recurrences	6
1-2 years later; reoperation + cobalt; well 10 years	
1-1 year later; reoperation; well 10 years	
1-3 years later; subtotal excision + cobalt	
Recurrence 5 years later; total excision + cobalt; well 5 years	
1-9 years after; Cobalt; well 1 year	
1-3 recurrences inspite of cobalt; last total excision; died of infarction	
1-4 years later; total excision; well 5 years	
1-1 year later; reservoir insertion	

*1 at 1 year, 3 at 2 years, 1 at 4 years, 1 at 5 years, and 2 at 10 years

TABLE XIIIA
RESULTS OF SUBTOTAL EXCISION

	Adults 13 cases all irradiated
Postoperative death	2
1 - Pulmonary embolism, 1 - Aneurysmal SAH	
No follow up	1
Delayed death	2
1 - A year later? cause, 1-3 years later, MI	
No recurrence	6
3 at 2 years, 1 at 7 years, 1 at 18 years	
Recurrence	2
1 - After 7 years; hypothalamic disturbance - died	
1 - After 3 months; Ommaya reservoir insertion - well for last 3 years	

TABLE XIIIB
RESULT OF SUBTOTAL EXCISION

	Children (17 cases)
Postoperative death (hypothalamic disturbances)	2
No follow up	2
Delayed death	5
1-2 months later of? hydrocephalus	
1-3 months later of? cause	
1-4 months later of? cause	
1-3 years later of? cause	
1-3 years later of trauma	
No recurrence (3 irradiated)	6
1-5 years, 1-6 years, 1-10 years, 1-14 years, 1-16 years, 1 - at 18 years	
Recurrence	2
1 - After 10 years; cobalt; well 4 years	
1-1 year later; subtotal excision twice, + cobalt: well last 10 years	

Most of the craniopharyngiomas were of a large size, none being of small size. Thirty-nine of them were large, 14 of giant size whereas only 3 were of medium size.

TABLE XIV
SURVIVAL VERSUS NATURE OF TUMOUR

Survival	Total excision			Subtotal excision			Total
	Cystic	Solid	Mixed	Cystic	Solid	Mixed	
2 years	6	2	10	5	2	13	38
5 years	3	2	5	1	2	6	19
10 years	1	1	4	1	1	4	12

TABLE XV
SURVIVAL VERSUS SITE OF TUMOUR

Survival	Medium	Large	Giant
2 years	2	36	10
5 years	1	18	3
10 years	0	2	1

TABLE XVIA: MORBIDITY: NEUROLOGICAL

Visual deterioration	6 (2)
3rd nerve paresis	7 (1)
Hemiparesis	9 (1)
Hypothalamic disturbances	
Hyperpyrexia, somnolence	4 (1)
Hydrocephalus	7
Shunt	5
Drain	2
Cerebral oedema	5
Aseptic meningitis	7
Infection	
Meningitis	2
Wound infection	1
Abscess	1
Convulsions	7
Subdural effusion	2
Pneumocephalus	1

TABLE XVIB
MORBIDITY: ENDOCRINOLOGICAL

Diabetes insipidus	0
SIADH	5
Hypoglycemia	2
Hypocortesemia	25
Hypothyroidism	11
Stunted growth	9
Hypogonadism	9
Loss of libido	1
Obesity	6

TABLE XVIIA
MORTALITY: OPERATIVE MORTALITY

Adults		Children	
Total excision	Subtotal excision	Total excision	Subtotal excision
1/6	2/13	1/17	2/17

6/53=11.3%

TABLE XVIIB
PROCEDURAL MORTALITY

Adults		Children	
Total excision	Subtotal excision	Total excision	Subtotal excision
1/6	2/13	1/26	2/19

6/64=9.38%

The lesion was essentially cystic in 18, mainly solid in 9 and of a mixed variety in 29 patients (Table VII).

Nature of Surgery (Table VIII)

Whenever possible, a total excision was attempted. A gross total excision was carried out in 23 patients, subtotal or partial excision in 31 patients whereas aspiration alone was carried out in 1 cystic craniopharyngioma as the patient had presented in a very poor neurological state.

Of the 17 cystic lesions, 8 could be totally excised, 8 had a subtotal excision and aspiration alone was carried out in one. Of the 9 solid lesions, 3 could be totally excised and 6 had a subtotal excision. Of the 20 of mixed variety, 10 were totally excised and 10 had subtotal excision.

Preoperative CSF diversion was carried out by insertion of a shunt in 5 patients whereas 1 had institution of external ventricular drainage. Postoperative shunting was needed in 5 and external ventricular drainage in 2 patients (Table IX).

Subfrontal approach was utilized in 43, pterional approach in 3, transcallosal in 2, transventricular in 3 and subtemporal approach in 2 cases (Table XA).

Twelve patients had a prefixed chiasma. The lamina terminalis approach was used in 8 and optico-carotid route in 4 patients.

Pituitary stalk could be preserved only in 2 patients.

Depending on the extent of excision of the tumour, its recurrence and associated hydrocephalus, multiple operative procedures became necessary in some of the patients. Fourteen patients who had a total excision and 23 with subtotal excision have needed only one procedure till now. Two with total excision and one with subtotal excision had a second craniotomy. One with total excision had 4 craniotomies., whereas 4 with total excision and 5 with subtotal excision had shunt insertion as well. Two patients, one with total and the other with subtotal excision had a reservoir insertion into the cystic recurrence (Table XI).

Results

The longest survivors after first surgery are two patients, an adult and a child, who have now survived for 17 years following a subtotal excision and cobalt therapy for cystic tumours.

Of the 6 adults who had a total excision of their tumours, 5 have had no recurrence, the follow up period being 1 at 1 ½ years, 3 at 3 years and 1 at seven years. One patient died of hypothalamic disturbances in the immediate postoperative period (Table XIIA).

Of the 17 children who had a total excision of their tumour, 8 have not had recurrence, the follow up period being 1 year for 1, 2 years for 3, 4 years for 1, 5 years for 1 and 10 years for 2 patients. There was one delayed death, the child having been operated elsewhere for possible recurrence. Seven children had a definite recurrence. One child, who had recurrence 2 years later was reoperated and subsequently subjected to radiation. He is well 10 years later and has grown up with hormonal replacement. One child had a recurrence a year later, had total excision for the recurrence and is now well 10 years later. Another child had a recurrence 3 years later when a subtotal excision was carried out and cobalt therapy given. The child again had a recurrence 5 years later when a total excision was carried out and further cobalt therapy given. The child is quite well now 5 years later. One child has recurrence 9 years later for which radiation has been given a year ago. Another child had a recurrence 4 years later when a total excision was carried out. The child is well now for over 5 years. One unfortunate child had 3 recurrences inspite of initial apparent total excision. Following the last procedure of total excision, the child developed infarction in the territory of internal carotid artery and died. One other child showed a cystic recurrence a year later. A reservoir with a catheter has been inserted. The child has had a couple of aspirations, since then (Table XIIB).

Eleven of the 13 adults who had a subtotal excision of their tumours were irradiated. Six of them did not have any recurrence with a follow up of 2 years for 3, 3 years for 1, 7 years for 1 and 18 years for 1. There were two deaths in the immediate postoperative period, one having died of pulmonary embolism and the other from an incidental aneurysm rupture. There were 2 delayed deaths, one having died of pulmonary embolism and the other of myocardial infarction 3 years later. There were two recurrences, one having died of hypothalamic disturbance after a recurrence 7 years later. The other patient had a recurrence of the cyst 3 months later; Ommaya reservoir and a catheter were inserted. He developed infection, the cyst got converted into an abscess. This was treated by repeated aspirations and instillation of gentamycin with a cure that has lasted over 3 years (Table XIIIA).

Of the 17 children with subtotal excision, 6 did not have any recurrence with a follow up of 5 years for 1, 6 years for 1, 10 years for 1, 14 years for 1, 16 years for 1 and 17 years for 1 patient. There were 2 recurrences. One that occurred after 10 years was irradiated and has been well for 4 years thereafter. The other had a recurrence 1 year later for which subtotal excision was carried out twice and cobalt therapy given. This child is well for 10 years thereafter. There were 2 deaths in the immediate postoperative period due to hypothalamic disturbances and also due to occurrence of meningitis in one of them. There were 5 delayed deaths. One

died 2 months later possibly of hydrocephalus that was not treated. The other 3 died, 3 months, 4 months and 3 years later of undetermined cause at their native place. One died 3 years later in a road accident (Table XIIIB).

One blind child who had a burr hole aspiration only, died 3 months later. Another child who had a burr hole aspiration of a cystic lesion followed by irradiation has been well 6 years later. One child who was critically ill, had insertion of an external ventricular drain only as he was unfit for major surgery. He did not show any recovery and died 2 days later.

The nature of the tumour, whether cystic, solid or mixed did not seem to make a significant difference in terms of feasibility of total excision (Table XIV).

The length of survival also did not seem to definitely depend on the nature of the lesion, though it seemed to be higher in the mixed variety of the lesion.

Five years and 10 years survival did not seem to depend on the type of surgery, the incidence being similar for total as well as subtotal excision.

The long term survival in a small tumour that is less than 1.5 cm in size would certainly be high as it can be totally removed with impunity in most of the cases (Table XV).

However, one should expect greater difficulty in the excision of larger tumour due to their adhesion to surrounding structures, the problem becoming more acute with giant tumours. Our experience, however, shows only a slight difference between 5 years survival in large versus giant tumours. Probably with a longer follow-up, the incidence of 10 years survival may be significantly higher in large tumours versus the giant tumours.

There was transient deterioration of vision in 6 patients with residual impairment in 2, transient third nerve paresis was observed in 7 patients whilst permanent only in 1. Transient hypothalamic disturbances were observed in 4 with residual in 1. Hydrocephalus needing shunt insertion or ventric drain occurred in 7, cerebral oedema in 5, aseptic meningitis in 7, subdural effusion in 2, pneumocephalus in 1, wound infection in 1, meningitis in 2, abscess formation in 1 and convulsions postoperatively in 7 patients (Table XVIA).

Thirty patients developed diabetes insipidus in the immediate postoperative period. The first manifestations appeared within 12 – 36 hours after the operation. Eighteen of these were controlled easily with 400 mg – 600 mg of Carbamazepine per day, whereas 12 needed additional injections of Pitressin for the first few days. Seven of these patients were left with permanent diabetes insipidus, needing Pitressin/DDAVP along with Carbamazepine. Five patients had developed SIADH within the first postoperative week needing active treatment. Hypocortesemia was found in 25 patients, 6 of whom have been kept on daily dose of steroids. Hypoglycemia was noted in 2 patients. Hyponatremia was not seen in any of the patients though a long term study of serum electrolytes was not carried out. Eleven patients developed hypothyroidism and needed substitution therapy. Growth was stunted in 9 children, 2 of whom were given Growth Hormone with substantial improvement. Hypogonadism was noted in 9 patients, 3 of whom were put on testosterone therapy. Obesity with increased appetite was found in 6 patients (Table XVIB)

Two out of 23 patients with total excision and 4 out of 30 patients with subtotal excision died within one month of operation giving a case operative mortality of 11.3%. However, some patients had two and three operative procedures for recurrence, a total of 64 procedures being carried out in all (Table XVIIA and Table XVIIB). The procedural mortality thus was 9.38%. This compares favourably with most of the published series, when one considers the fact that most of the lesions were either large or giant in size.

Discussion

Total excision of the tumour is possible as well as safe when it is small in size and essentially prechiasmatic in location. In the present series, there were only 3 cases with tumour that were less than 3.0 cm in size whereas 14 were more than 5.0 cm in size and multicompartmental. Twelve of them were retrochiasmatic in location with a prefixed chiasma. These patients would be more liable to hypothalamic disturbances and metabolic problems when a total excision is attempted.

Though one gets the impression that it would be easier to excise a cystic lesion totally, we did not find much difference between the excisability of a cystic versus a totally solid lesion. Partly calcified wall of the cystic lesion seemed to have adhesions to the blood vessels and at times one had to leave behind a small adherent part of the capsule. More lesions of mixed nature could be totally excised. A solid rock of calcium was difficult to remove, especially when it was retrochiasmatic. Hoffmann (1982) has found laser to be extremely useful in fragmenting calcium and enabling their total excision. Radical total excision of a multicompartmental craniopharyngioma also posed a difficult problem.

We have found a subfrontal approach, either unilateral or bilateral, to be more suitable for excising a majority of these tumours. In the lesions that are essentially intra-third ventricular, a transcallosal or transventricular was useful; in those with a prefixed chiasma, a translaminar approach seemed ideal. We excised 8 such tumours through a translaminar approach (1990) and 4 through

a optico-carotid approach. Hoffmann *et al*. (1992) have used translaminar approach to aid in resection of the retrochiasmatic tumour in 18 patients. We have not used the rail-road approach suggested by Patterson and Danylwich (1980) of combining translaminar with transsphenoid approach. A subtemporal approach would be useful in excising a lesion that is located in the parasellar region as well as the posterior fossa.

Twenty three patients were considered to have had a total excision of the tumour at the time of surgery whereas thirty had subtotal tumour excision and two had aspiration of the cystic component. Thirteen of the twenty three patients who had a total excision have not had a recurrence in the follow up period between 3 years to 12 years (mean 6.12 years). However, six patients who were thought to have a total excision of the tumour had a recurrence within 4 years of the operation whereas one patient had a recurrence as late as 9 years after the operation. The recurrence was detected on CT scanning when the patients complained of headache and deterioration in vision. This goes to show that inspite of apparent total excision that one sees on the operation table, the patients need to be followed closely for a possible recurrence. CT scan with contrast should be obtained atleast 6-8 weeks after the operation to detect any residue of the tumour, and should be repeated once a year for the first few years and at the slightest occurrence of headache, visual impairment or diabetes insipidus. Even a flake of calcium left in the sella can be a starting point for a recurrence at a later date. Seventeen of the Hoffmann's (1989) forty five patients had a tumour recurrence after what was believed to be a total excision.

Biological behaviour of the tumour seemed to be different in adults and children who had a total excision of the tumour whereas no adult who had a total excision had a recurrence of the tumour. Also, a couple of children who had a near total excision of their multicompartmental tumours showed a massive recurrence of the tumour within a few months of their initial surgery. None of the adults had such a rapid regrowth of their residual tumour. One child had a recurrence of the tumour twice whereas the other had recurrence of the tumour thrice inspite of an apparent total excision twice.

In two children who had a recurrence of their tumour, one year and four years after an apparent total excision, a total excision could be achieved at a second operation. They are recurrence free, twelve and seven years postoperatively. It was possible to achieve a total excision of the tumour in one child who had two subtotal excisions and cobalt therapy earlier. The child is well for seven years thereafter. Hoffmann (1982) could remove the tumour totally in five of their patients who had recurrence after initial surgery. Total excision of the tumour in these patients did not seem to pose further difficulties due to adhesions from previous surgery. Therefore, an attempt should always be made to carry out a total excision of the tumour at reoperation. Carmel *et al*. (1992) could achieve total excision in 67% of their reoperated patients.

Three of the children who had a recurrence of the tumour after an apparent total excision were subjected to cobalt therapy. Two of them had subtotal excision of the recurrence before irradiation. They have not had a recurrence of the tumour through seven and twelve years after cobalt therapy. Six of the adult patients and three of the children with subtotal excision who had received cobalt therapy have remained free from tumour recurrence between 4 years and 13 years (mean 9.2 years). Two of the children who had recurrence after subtotal excision have remained well for 6 and 12 years after irradiation. Thus we found irradiation to be a useful tool in our armamentarium in tackling craniopharyngiomas that cannot be excised totally or recur, a view shared by many authors (Amacher 1980, Fischer 1990, Karamer 1976, Manaka *et al*. 1985, Shillito 1985). We therefore would recommend irradiation in craniopharyngiomas that cannot be totally excised even though there are hazards of radiotherapy. There are increasing number of reports of occurrence of tumours like gliomas (Sogg *et al*. 1978, Ushio *et al*. 1987, Waga and Handa 1976) and meningiomas in the path of radiation or setting in of mental retardation. Stereotaxic intra-cavity radiation with yttirium-90 (Amacher 1980) for cystic craniopharyngiomas is also reported to be fairly useful in their management, nearly 60% of the tumours remaining remission free for varying lengths of time. Stereotaxic radiosurgery (Backlünd 1973, 1989) is also found to be effective in treating smaller solid craniopharyngiomas.

We did not find a significant difference in the postoperative endocrinological and metabolic disturbances between those with total and subtotal excision of the tumour except for hypocortisemia that was more frequent in patients with total excision. Though Maurice Choux found the incidence of diabetes insipidus to be twice as much in patients whose stalk was cut, we did not find sectioning or otherwise of the pituitary stalk to alter the incidence of diabetes insipidus in the immediate postoperative period. Those who developed complication permanently required regular doses of Pitressin/DDAVP. SIADH occurred infrequently in our series, often insidiously, after a vigorous management of diabetes insipidus in the initial post-operative period, requiring a total change in the management of the patient.

Conclusions

Management of craniopharyngioma still remains a controversial issue. Total excision whenever feasible, seems to be the ideal mode of treatment. If total excision were not feasible one should settle for subtotal excision followed by radiotherapy. Frequent follow up clinically as well as by regular CT scans is essential to detect a recurrence after a "total excision". The recurrence may be reoperated and further attempts be made for total excision. If this is not possible, irradiation, either with external beam or radiosurgery would be worthwhile. Nearly 80% of patients respond well to irradiation. With the advent of steroid therapy, modern tools like CUSA and laser, and microsurgical techniques, surgery has become much safer and less hazardous.

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