Pediatric Craniopharyngiomas: A Primer for the Skull Base Surgeon

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Abstract

Pediatric craniopharyngioma is a rare sellar-region epithelial tumor that, in spite of its typically benign pathology, has the potential to be clinically devastating, and presents a host of formidable management challenges for the skull base surgeon. Strategies in craniopharyngioma care have been the cause of considerable controversy, with respect to both philosophical and technical issues. Key questions remain unresolved, and include optimizing extent-of-resection goals; the ideal radiation modality and its role as an alternative, adjuvant, or salvage treatment; appropriate indications for expanded endoscopic endonasal surgery as an alternative to transcranial microsurgery; risks and benefits of skull base techniques in a pediatric population; benefits of and indications for intracavitary therapies; and the preferred management of common treatment complications. Correspondingly, we sought to review the preceding basic science and clinical outcomes literature on pediatric craniopharyngioma, so as to synthesize overarching recommendations, highlight major points of evidence and their conflicts, and assemble a general algorithm for skull base surgeons to use in tailoring treatment plans to the individual patient, tumor, and clinical course. In general terms, we concluded that safe, maximal, hypothalamic-sparing resection provides very good tumor control while minimizing severe deficits. Endoscopic endonasal, intraventricular, and transcranial skull base technique all have clear roles in the armamentarium, alongside standard craniotomies; these roles frequently overlap, and may be further optimized by using the approaches in adaptive combinations. Where aggressive subtotal resection is achieved, patients should be closely followed, with radiation initiated at the time of progression or recurrence—ideally via proton beam therapy, although three-dimensional conformal radiotherapy, intensity-modulated radiotherapy, and stereotactic radiosurgery are very appropriate in a range of circumstances, governed by access, patient age, disease architecture, and character of the recurrence. Perhaps most importantly, outcomes appear to be optimized by consolidated, multidisciplinary care. As such, we recommend treatment in highly experienced centers wherever possible, and emphasize the importance of longitudinal follow-up—particularly given the high incidence of recurrences and complications in a benign disease that effects a young patient population at risk of severe morbidity from hypothalamic or pituitary injury in childhood.

Keywords

- pediatric craniopharyngioma
- skull base
- transsphenoidal surgery
- radiotherapy
- stereotactic radiosurgery
- proton beam
- pituitary injury
- hypothalamic injury

Introduction

Pediatric craniopharyngioma is a challenging neuro-oncologic entity, the optimal management of which has been regularly debated and revised over several generations of surgeons. This is due at once to its unpredictable and often refractory natural history, as well as our evolving understanding of the long-term sequelae of various treatment algorithms, and shifting attitudes toward goals-of-care. In parallel, therapeutics have improved significantly via

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advances in microsurgical and endoscopic tools and technique, supplemental technologies such as intraoperative magnetic resonance imaging (MRI) and high fidelity stereotaxis, and the development of advanced radiotherapy (RT) modalities including three-dimensional conformal RT (CRT) and proton beam radiotherapy (PBRT). Taken together, these variables have rendered a complex calculus, requiring that treatment paradigms be detailed to the individual patient and tumor, with a host of clinical factors carrying weight. Given the frequent involvement of anterior and middle fossa structures including the hypophyseal–pituitary axis, visual apparatus, named vessels of the skull base and their perforators, and the cavernous sinus, surgical engagement with these tumors frequently requires skull base techniques. Correspondingly, our aim was to survey the literature on this rare but critically important pediatric tumor, with the goal of establishing a contemporary treatment algorithm, and highlighting areas of particular interest to the skull base community.

Demographics and Epidemiology

Pediatric craniopharyngioma is an uncommon tumor, comprising 6% to 9% of all pediatric central nervous system neoplasms.[1–3] In spite of this relative rarity, craniopharyngioma remains the most common pediatric nonglial tumor, and accounts for 3% of intracranial tumors in all age groups.[4,5] Overall incidence of craniopharyngioma is low, with ~1 to 2 new cases diagnosed annually per million people, and a bimodal distribution peaking between the ages of 5 to 14 and 50 to 75 years, with a roughly equal distribution between children and adults.[6]

Data regarding sex distribution have been equivocal, with most authors finding no significant difference, or a minimal increase in male incidence, with ratios ranging from 0.9 to 1.6 male-to-female patients.[7–10] Geographic distributions have been less well characterized. Recent survey data highlight an international variability in incidence ranging from 1.5% to 11.6%, potentially suggestive of underlying environmental factors; however, the reliability of these estimates and the confounding influence of socioeconomic conditions make it impossible to confirm if these differences are accurate.[11]

Long-term population-level survival data after diagnosis of craniopharyngioma is limited to the Finish Cancer Registry, which reported a 5-year overall survival rate of 69% among all patients entered into the database 1951 to 1982, with improvement to 73% among those patients diagnosed after 1970.[12] Within the US population, the National Cancer Database describes overall survival in excess of 80% in several cohorts; however, when stratified by age, 5-year survival for patients less than 20 years old approached 99%, as compared with 38% among those patients aged 65 years and above.[8] This correlates with the findings of most preceding surgical series, which overwhelmingly report 5-year survival in the range of 90% to 100% in children.[13] Studies that have compared large-scale survival over time have noted significant gains, most likely attributable to improvements in treatment protocols and surgical techniques, such as the German Childhood Cancer Registry, which demonstrated an increase in 5-year survival from 91% during 1980 to 1989, to 98% from 1990 to 1999.[14,15]

Pathologic, Molecular, Genomic, and Transcriptomic Characteristics

The pathologic origins of craniopharyngioma remain incompletely understood, although most authors agree that a sellar or parasellar embryonal remnant underlies the neoplasm—arising either from ectodermal remnants of the Rathke cleft and pouch or from residual embryonal hypophyseal epithelium.[5,7,16] Two major histologic subtypes have been described—adamantinomatous and papillary—with cystic adamantinomatous tumors comprising the overwhelming majority of pediatric disease, although both mixed tumors and neoplasms containing concomitant areas of craniopharyngioma and Rathke cleft cyst have been reported in children.[4,5,7,17] Classic descriptions of adamantinomatous craniopharyngioma highlight central whorls and cords surrounded by stellate reticulum, "wet" keratin, and palisading columnar epithelium (►**Fig. 1**).[4,5] Among adults, adamantinomatous lesions still predominate, with papillary histology comprising 14% to 50% of all tumors.[6] Of note, this binary may have significant molecular underpinnings associated with β-catenin mutations, which are identified in over 70% of adamantinomatous craniopharyngiomas, but have not been observed in papillary tumors or Rathke cleft cysts.[18–23]

Looking more closely at other prominent pathologic molecular markers, although the discovery of *BRAF V600E* mutations in papillary tumors generated considerable interest in the use of BRAF inhibitors such as vemurafenib for adults, the identification of candidate genes in pediatric adamantinomatous craniopharyngioma has been more frustrating.[24,25] The most widely observed mutation, *CTNNB1*, occurs in more than 90% of adamantinomatous craniopharyngiomas, and results in abnormal accumulation of β-catenin, an important player in canonical Wnt signaling pathway and therefore cell differentiation and proliferation.[25,26] This may provide a useful disease marker—inroads are currently being made toward serum-based cell free deoxyribonucleic acid (DNA) assays, which may lead to biopsy-free diagnostic testing—however, β-catenin is a nearly universal player in cellular homeostasis, and the development of specific Wnt pathway inhibitors has been challenging.[24,26]

Other studies have demonstrated increased expression of both sonic hedgehog (SHH) and its receptor PTCH1 in adamantinomatous craniopharyngioma, often in patterns correlating with epithelial palisades and co-localizing with β-catenin, indicating a potential autocrine–paracrine mechanism.[26] Vismodegib is a smoothened inhibitor that acts on the SHH pathway and is FDA approved for the treatment of basal-cell carcinoma, as well as undergoing active clinical trials in pediatric medulloblastoma.[27] Pending their results, as well as those of ongoing preclinical animal studies, it may present a promising avenue for targeted therapy in adamantinomatous craniopharyngioma.[24,26] Still other investigations have highlighted epidermal growth factor receptor (EGFR)

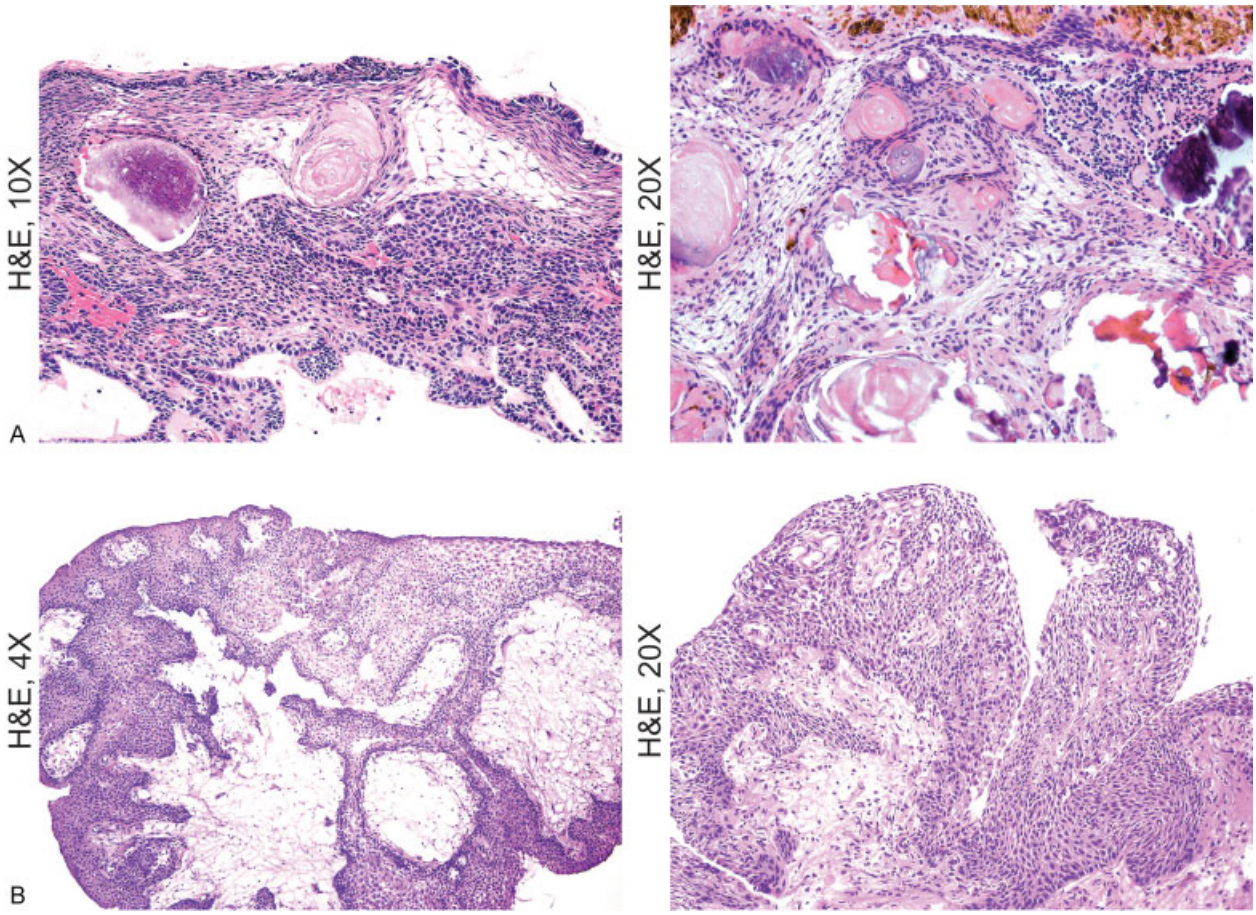

Fig. 1 Hematoxylin and eosin (H&E) histopathologic photomicrographs at 10X and 20X demonstrate characteristic features of adamantinomatous pediatric craniopharyngioma (**A**), which include central whorl and cords surrounded by stellate reticulum, "wet" keratin, Rosenthal fibers, and palisading columnar epithelium. By contrast, photomicrographs of adult papillary craniopharyngioma at 4X and 20X (**B**) are marked by a solid, well-circumscribed epithelial architecture with distinct pseudopapillae, absent zones of loose stellate reticulum or "wet" keratin, and a general resemblance to other metaplastic squamous epithelia.

abnormalities as potentially important to tumorigenesis. EGF pathway gene activation has been demonstrated in the adamantinomatous craniopharyngioma transcriptome, as has augmented EGFR nuclear colocalization with β-catenin the infiltrating tumor border—where Wnt activity is similarly increased, collectively stimulating abnormal cell growth and migration.[25,28–32] At present, several EGFR inhibitors have been developed and approved for use in lung cancer treatment, most prominently gefitinib. In vitro studies have indicated that this may be an avenue for future development; however, preclinical animal studies and human trials remain unreported at present.[24,29]

Less well understood still is the role of the local inflammatory microenvironment in craniopharyngioma development. As with most neoplastic processes, a wide swath of abnormalities has been identified, including elevated interleukin 6 (IL-6), IL1α, tumor necrosis factor, and α-defensin 1to 3 levels in the cyst fluid, and upregulated CXCR4 and CXCL12 in recurrent tumors.[24,33–36] Each of these may present a potential avenue for targeted therapy, particularly given the breadth of pharmacologic and biologic agents available or in development; notwithstanding, whether this tumor-associated inflammation is pro- or antitumorigenic remains to be established, as does the general safety and efficacy of immunomodulatory treatment strategies in craniopharyngioma.

Genome-wide transcriptome analysis was first applied to craniopharyngioma biology by Gump et al in 2015, in a study of 15 adamantinomatous tumors, followed by a second study of 18 adamantinomatous and 10 papillary craniopharyngioma published by Hölsken et al in 2016.[28,37] Taken together, these studies further emphasized the central role of Wnt and SHH abnormalities, with findings including DNA hypomethylation of *AXIN2*, *GLI1*, and *PTCH1*. EGFR pathway genes were also once again implicated, as were a host of other novel genes with diverse roles including IL-2B, MMP12, EphA2, and LCK.[24,28] Further investigations are clearly required to establish even a preliminary understanding of the roles these candidate genes play in craniopharyngioma pathophysiology; however, each signals a possible target for future therapies.

Treatment Considerations

Imaging Characteristics

Located along the central skull base, with a typical center in the sella or suprasellar region, craniopharyngiomas are

characteristically complex, often including polycystic architecture containing a wide swath of signal intensity and enhancement patterns (►**Fig. 2**).[38,39] Classically, the defining radiographic features of a craniopharyngioma have been cyst formation, enhancement of the solid tumor components, and calcification, each of which is observed in at least 80% of tumors.[39,40] This is particularly the case among pediatric tumors, as the dominance of adamantinomatous disease results in an even higher prevalence of large, lobulated cysts comprising the bulk of the tumor mass.[40]

Although MRI provides the backbone of craniopharyngioma imaging, noncontrast head CT is an important adjunct—and with respect to characterizing the presence and extent of calcification, the preferred modality. CT also helpfully distinguishes cysts that are high-intensity on MRI from solid tumor, as cyst fluid is consistently (though not universally) low density on CT imaging.[41]

Among pediatric patients, calcification in the presence of cyst formation in a mixed-density sellar-region tumor is diagnostic of craniopharyngioma. In the absence of calcification, however, the differential may include pituitary adenoma, germinoma, hypothalamic glioma, and other very rare neoplasms.[42] If supplemental testing such as cerebrospinal fluid (CSF) studies for tumor markers is not revealing, proton

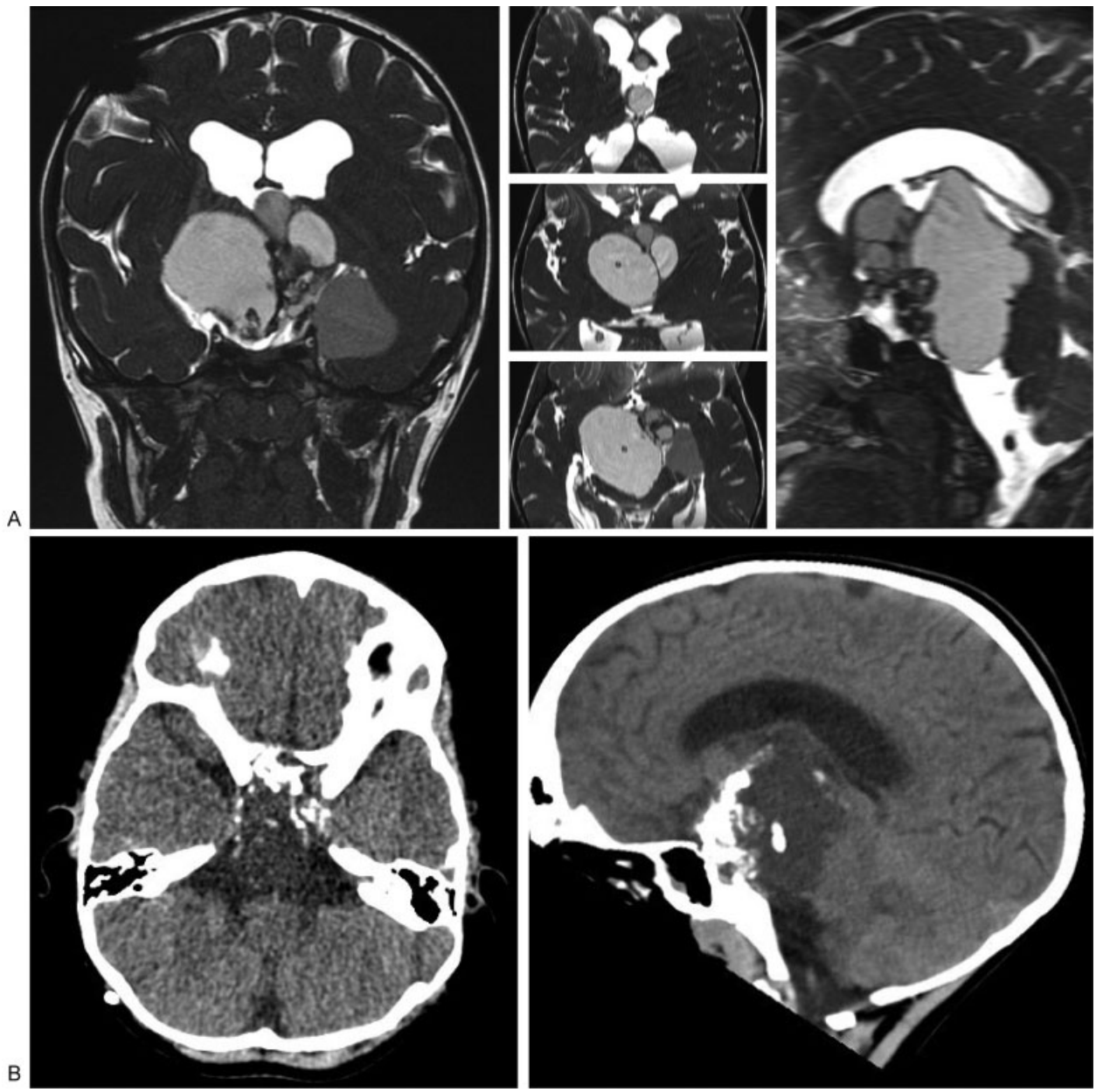

Fig. 2 T2-weighted magnetic resonance imaging of the brain in the coronal, axial, and sagittal planes (**A**) demonstrates a complex, polycystic, mixed density mass centered about the sella, with significant extension into the third and lateral ventricles, interpeduncular and prepontine cisterns, and temporal lobe, as well as presence of a highly compressed cavum septum pellucidum, and a right frontal cystoperitoneal shunt. Nonenhanced head computed tomography demonstrates robust and diffuse calcification of the sellar and parasellar mass (**B**), diagnostic of craniopharyngioma in a pediatric patient.

MR spectroscopy may be useful, given the unique craniopharyngioma signature characterized by a single, dominant lipid-lactate peak (as compared high choline-to-*N*-acetylaspartate ratio observed in glioma, and the bland signature of pituitary adenoma).[42]

Tumor location is derived from the embryonic pathway of the craniopharyngeal duct, resulting in 95% of tumors containing a suprasellar component, of which approximately two thirds also demonstrate intrasellar extension. Exclusively intrasellar lesions are uncommon (5%), while purely intraventricular tumors are exceedingly rare, and almost exclusively occur in adults with papillary disease.[38,43,44] Obstructive hydrocephalus is a common finding at diagnosis, noted on initial imaging in up to 54% of pediatric tumors, as is encasement of the circle-of-Willis vessels and their major branches, each of which may have significant implications in terms of preoperative planning.[38]

Extent-of-Resection

Early studies of craniopharyngioma were based on the presumed philosophy that aggressive surgery was the standard-of-care, and indeed, a significant number of retrospective and prospective clinical studies observed extent-of-resection to be the most important factor contributing to long-term local control, with 10-year recurrence rates after gross total resection (GTR) ranging from 0% to 50%, as compared with 25% to 100% after subtotal resection (STR).[7,13,38,45] Correspondingly, most preceding authors have traditionally advocated radical surgery, and argued that simultaneous improvements in medical treatments for endocrinologic injury and microsurgical technique tip the overall balance in favor of aggressive resection.[46–48] However, as advanced radiation technologies including intensity-modulated radiation therapy (IMRT), CRT, and PBRT have evolved, several authors have demonstrated that STR followed by RT may be a preferable strategy, shifting the overarching treatment paradigm.[15,49–53] Ali et al have demonstrated that, with respect to quality-of-life, better outcomes are inversely related to extent-of-resection, with the best results achieved after a limited biopsy and conformal RT.[54]

With this conflict in mind, various authors have attempted to establish clinically meaningful radiographic classifications schemes, with the goal of setting preoperative resection goals to reduce operative morbidity. Puget et al described a three-tier system in which the tumor is categorized as (1) clearly not involving the hypothalamus, (2) abutting or displacing the hypothalamus, or (3) clearly involving the hypothalamus (defined as the absence of anatomically distinct hypothalamus).[55] Respectively, treatment was then performed based on that classification: group A patients underwent attempted GTR, group B patients underwent planned near-total resection (maximal resection without engagement of the hypothalamus) followed by RT, and group C patients underwent planned STR followed by RT. Using this protocol, they had zero cases of hyperphagia/morbid obesity—the most feared complication of aggressive surgery—or behavioral dysfunction, in a prospective cohort of 22 children followed for a mean 1.2 years postoperatively. Although the short follow-up period precludes consideration of long-term RT complications, preceding analyses have demonstrated significant improvements in quality-of-life when pediatric craniopharyngioma is treated via planned STR and adjuvant RT, as compared with GTR; by extension, we infer that the approach recommended by Puget et al may provide an optimized algorithm for preoperative planning, although more definitive conclusions are pending long-term follow-up outcomes in a larger prospective cohort.[49,54,56]

Transsphenoidal Resection: Limitations in the Pediatric Population, and Potential Advantages of the Endoscopic Endonasal Approach

Another key area of active debate in the management of pediatric craniopharyngioma is the role of transsphenoidal surgery. Although a growing number of studies have examined this critical question in adult populations, no study has yet to directly compare postoperative outcomes after open or transsphenoidal resection of craniopharyngioma in a pediatric population. Correspondingly, current clinical recommendations are largely based on extrapolations derived either from the adult craniopharyngioma literature or more general studies of transsphenoidal surgery in children.

Among the essential, baseline considerations relevant to any transsphenoidal craniopharyngioma resection in the pediatric population are the impact of sinus pneumatization on the size and availability of a useful operative corridor. Radiographic studies have demonstrated that initiation of sphenoid pneumatization occurs between 6 months and 4 years, and is complete between 9 and 12 years.[57–59] As such, transsphenoidal approaches are more challenging in children aged fewer than 9 years, with perhaps the specific exceptions of a biopsy or cyst fenestration in a young child with early pneumatization.[60–62]

Given these anatomic limitations, prior to the development of the endoscopic endonasal approach (EEA) and its extended variants, microsurgical transsphenoidal resection was largely reserved for intrasellar craniopharyngiomas, or tumors with minimal, midline extension beyond the subdiaphragmatic space.[63–65] The implications of this fundamental distinction in pediatric patients selected for transsphenoidal versus transcranial craniopharyngioma resections were realized in the meta-analysis performed by Elliott et al .[66] Perhaps unsurprisingly, given that the vast majority of the transsphenoidal operations included in their meta-analysis were for small, intrasellar tumors, their chief conclusion was that significant selection bias was present between the cohorts, and that a valid comparison could not be performed. Notwithstanding, their findings did suggest that transsphenoidal resection presented a safe option for resection of pediatric craniopharyngioma, with the understanding that those results were based on an optimized cohort. However, within the past decade, advances in endoscopic techniques and equipment have empowered surgeons to successfully engage almost all midline craniopharyngiomas—including those with significant suprasellar, supradiaphragmatic, or intraventricular extension.[67–75] Correspondingly, we expect that the role of EEA in

the resection of pediatric craniopharyngiomas will continue to expand, and the key lessons learned from both the adult population and the application of EEA to other pediatric lesions warrant more detailed review here.

The most extensive and relevant study of EEA for craniopharyngioma resection was published by Cavallo et al in 2014, which reported outcomes in 103 patients, including 20 children.[76] In their results, no significant differences were observed between children and adults with respect to extent-of-resection, or endocrine outcomes, and the rate of improvement in postoperative visual function was higher within the pediatric cohort (92% versus 71%). In spite of 75% of tumors having supradiaphragmatic extension, GTR was achieved in 70% overall (92% in primary resections; 38% in revision operations), and overall rates of worsened anterior pituitary function were ~50%—comparable to preceding outcomes observed after transcranial resections of large pediatric craniopharyngiomas.[65,66,76]

Perhaps the most important advantage in considering an EEA for craniopharyngioma resection is clear visualization of the retrochiasmatic space and inferior hypothalamus—both of which are often involved with tumor, risk significant morbidity, and are often inadequately accessed via anterior transcranial approaches.[65,77,78] By turn, tumors with extensive superior or lateral extension into the interhemispheric or Sylvian fissures are poorly managed via EEA, and require either a transcranial or combined approach, based on their overall architecture.[65] Interestingly, several authors have also demonstrated that a pronounced learning curve exists in the adoption of EEA techniques, appreciable at both the level of individual surgeons and the skull base community at large.[79,80] CSF leak remains the most pronounced disadvantage of EEA when compared with transcranial approaches; however, early data likely overestimated this risk, as reconstructive techniques centered around vascularized, pedicled nasoseptal flaps and multilayer repairs were not yet standard-of-care, and in experienced hands the actual risk is more accurately estimated at 1% to 5%.[62,65,77,79,81]

Although evidence regarding EEA for pediatric craniopharyngioma resection is limited, several broader series reporting EEA outcomes in more general pediatric populations have been published, the largest of which is a series of 133 patients by Chivukula et al from 2013.[82] In their heterogeneous review, which included angiofibromas, craniopharyngiomas, pituitary adenomas, chordomas, chondrosarcomas, dermoids, epidermoids, and several other rare neoplasms and congenital malformations, outcomes were favorable overall. GTR was achieved in 58%, and near-total resection in another 28%; 57% had symptom resolution and 31% had at least some improvement in presenting neurologic symptoms; diabetes insipidus (DI) was the most common complication occurring in 20 patients (15%), of whom 12 had permanent DI; and postoperative CSF leaks occurred in 14 (11%), a notable increase from the expected rate, but as described above, one that is potentially skewed by changes in standard-of-care within a study population that spanned 1999 to 2011. Other comparable series by Rigante et al, de Divitiis et al, and others documented similar results, all collectively demonstrating that, in appropriately selected patients with favorable anatomy, EEA is a compelling option for the resection of pediatric craniopharyngioma, and a marked improvement on the microscopic transsphenoidal approach for tumors with significant extension beyond the sella.[83,84]

The Role of Other Skull Base Techniques

In patients for whom the transsphenoidal route is suboptimal, either due to the anatomy of the tumor or the patient's sinuses, a host of other skull base and general transcranial approaches can be employed to provide an optimal operative trajectory. Broadly, these can be grouped into anterior, intraventricular, and lateral approaches—each of which may be considered alone, or in combination with other transcranial or transsphenoidal techniques.

Anterior options can be further subcategorized into the midline anterior trajectories, exemplified by the bifrontal transbasal approach, and anterolateral trajectories, which include the standard pterional craniotomy and its common variants, including the orbitozygomatic and lateral supraorbital.[65] Midline anterior approaches are optimal for large, high, midline tumors with extensive third ventricular extension, and particularly in patients whose normal anatomy is such that the inferior corridor between the chiasm and diaphragm sella is especially narrow.[65] Similarly, opening of the lamina terminalis allows for optimal visualization of hypothalamus and third ventricle, and access to the interpeduncular, opticocarotid, and carotidoculomotor cisterns is straightforward via the transbasal approach. By contrast, the retrochiasmatic space is practically inaccessible from this trajectory, and tumors with significant components in this region are likely better attacked via an alternative approach.

The anterolateral approaches exploit the transsylvian and subfrontal trajectories to provide a relatively minimized working distance to the bilateral para- and suprasellar regions.[65] Among their greatest strengths is familiarity, as workhorse craniotomies employed by nearly all cranial neurosurgeons, given their efficiency, safety, and relative utility in a wide array of circumstances. Tumors with extensive Sylvian extension are optimal for an anterolateral approach; management of those individuals with both Sylvian and intra-ventricular disease will benefit from the addition of an orbitozygomatic osteotomy that allows significantly more inferior to superior angulation, whereas tumors that remain limited to the suprasellar and Sylvian spaces may be accessible via more minimally invasive techniques, including the lateral supraorbital and eyebrow craniotomies.

Intraventricular approaches are subdivided into two major subgroups, interhemispheric and transcortical, which have been compared frequently in the past.[85–90] Preceding findings with respect to the differences in the risk of perioperative stroke or seizure have been largely equivocal; however, our practice generally favors the interhemispheric approach, given the excellent access to the bilateral lateral ventricles, minimization of brain retraction, and optimization for a four-hands microsurgical technique. For tumors with lateral and third ventricular extension, the interhemispheric transcallosal trajectory can be further extended

inferiorly using a transchoroidal approach, which provides a safe, wide corridor into the third ventricle via posterior expansion of the foramen of Monro using the choroidal fissure—and, as necessary, through the tuber cinereum or lamina terminals from there. As one would expect, the chief limitation of any intraventricular approach is access to the anterior suprasellar space: and correspondingly these techniques are largely reserved for purely third ventricular craniopharyngiomas, or tumors whose extension predominantly expands along a superior–inferior trajectory centered about the anterior third ventricle.[65] Additionally, the risks of forniceal injury, pericallosal artery injury, and postoperative seizures, although frequently overstated, remain important considerations.[87,89,90]

True lateral skull base techniques are less frequently employed in craniopharyngioma surgery, yet even in their rarity, they present an important alternative means to access the retrochiasmatic space in patients for whom an EEA is a poor choice. In particular, transpetrosal approaches have been advocated by Al-Mefty et al as ideal trajectories for large or giant retrochiasmatic tumors in children, contrasting their wide corridors and extensive reach in multiple planes with the relatively limited windows allowed via transsylvian or transsphenoidal approaches, as well as the more direct obstacles presented by perforators and the optic apparatus when retrochiasmatic tumors are approached anterolaterally.[91] Of particular interest, they also demonstrated that the relatively diminished mastoid pneumatization of young children does not present a meaningful operative limitation, as it does with respect to the sphenoid sinus in planning a transsphenoidal approach.[91,92]

Poorly studied are the long-term cosmetic consequences of skull base approaches in children, in particular the orbitozygomatic craniotomy. Although a variety of adult studies have demonstrated that, with proper technique, excellent cosmetic outcomes can be achieved in spite of the inherently increased risks of the extensive exposure, these endpoints have only been subjectively reported and not objectively studied in pediatric populations.[93–95] Preliminary data are promising, and suggest that the orbitozygomatic craniotomy and its modified forms can be applied in children without significant long-term cosmetic implications.[96,97]

Overview of Radiotherapy

RT is an essential component of the pediatric craniopharyngioma treatment algorithm, with an increasingly prominent role as radiation technology has improved in parallel with an increased awareness of quality-of-life outcomes, collectively shifting the paradigm more in favor of planned STR followed by RT. RT modalities can be conceptually sorted into several major subgroups, which include traditional external beam RT (EBRT) and its more dynamic variants CRT and IMRT, highly targeted stereotactic single fraction or hypofractionated (1–5 fractions) stereotactic radiosurgery (SRS), as well as heavy particle-based systems such as PBRT.

No phase III data exists comparing STR with and without RT; however, at least four major series have compared STR alone with STR followed by EBRT, all of which demonstrated a significant reduction in tumor recurrence, with rates ranging from 55% to 86% absent RT, versus 0% to 20% after adjuvant treatment.[98–101] Although most publications were derived from treatment paradigms favoring GTR as the surgical treatment goal, the high prevalence of STR in all series allows a qualified extrapolation of their results to planned STR, with the presumption that complication results would most likely be noninferior (and potentially superior). Interestingly, related studies focused on the timing of EBRT failed to demonstrate an advantage to initiating adjuvant therapy in the early postoperative period, as opposed to at the time of progression.[99,100,102–104] Theoretically, this provides compelling support for delaying RT until tumor progression, particularly given the significantly increased cognitive risks of early RT in pediatric patients. Accordingly, in most children aged fewer than 4 years (including STR), we defer radiation until recurrence or progression has been proven, rather than immediately initiating adjuvant treatment. Unfortunately, given that the median time to progression is 12 months after STR in pediatric craniopharyngioma, the meaningful benefit of this delay in therapy is likely minimal.[105]

In terms of dose planning, prior results have not definitively proven a dose–response relationship in craniopharyngioma RT, with the majority of series demonstrating excellent local control (and no dose clear response effect) in the range of 54 to 55.8Gy, typically administered in 1 to 2 Gy daily fractions.[99,100,102,106–109] CRT and IMRT have become the standard-of-care as a means of reducing treatment volume, with at least one phase II trial reported by Merchant et al demonstrating equivalent local control with 90% 3-year progression-free survival and decreased treatment morbidity.[110] Several other institutional series have reproduced even more favorable results, with local control rate increasing from 56% to 78% to 85% to 96% when EBRT was replaced with CRT, as well as decreased overall treatment morbidity.[7,106,111]

SRS is a technique aimed at minimizing treatment effect beyond the lesion. Several authors have explored its utility as the primary RT modality in pediatric craniopharyngioma, with local control rates ranging from 78% to 100% at 1 to 3 years, and 65% to 85% at 5 years, at a typical dose of 12 to 13 Gy to the 50% isodose line.[112–117] However, in spite of these promising results, the applicability of SRS as the primary RT modality in SRS is limited both by tumor size and proximity to radiosensitive structures, most notably the optic nerves and chiasm.[118] In the postoperative setting, there may be difficulty in discriminating between tumor and postoperative changes, increasing the risk of either undertreating residual disease or inadvertently treating healthy adjacent tissue.[7] Efforts to mitigate possible risks of single fraction SRS have included fractionated SRS; although the logistic and emotional challenges of daily SRS for pediatric patients are not negligible, several series have convincingly demonstrated equivalent local control rates in excess of 90%, with decreased treatment morbidity as compared with both single fraction SRS and EBRT.[119–125]

PBRT and other heavy particles have attracted considerable interest in the treatment of pediatric craniopharyngioma, given the very sharp dose fall-off beyond the Bragg

peak, which translates to dramatically minimized radiation to healthy adjacent tissue—an important consideration in both a pediatric population and a tumor that abuts the optic apparatus.[111,126,127] Multiple prior authors have demonstrated excellent long-term local control with PBRT, including Fitzek et al, who reported zero recurrences in five patients followed for a median 13.1 years.[128–130] By contrast, Bishop et al failed to demonstrate superiority of PBRT versus IMRT with respect to either local control or overall survival. Importantly, access to treatment facilities can be limiting, although the modality is in its relative infancy, PBRT is in clinical trial for pediatric craniopharyngioma (NCT02792582, NCT01419067), and early data suggest that it may ultimately become the standard-of-care.[128,131]

An active frontier in RT for pediatric craniopharyngioma is pharmacologic priming to optimize tumor radiosensitivity. Although results are preliminary, they integrate the findings discussed above regarding pathologic EGFR activation, which is associated with radioresistance in other intracranial neoplasms including glioma, as well as with craniopharyngioma proliferation and recurrence, as discussed above.[29,132–136] In vitro analysis demonstrated that human adamantinomatous craniopharyngioma cultures underwent significantly increased cell death when RT was preceded by tyrosine kinase inhibition using gefitinib or CUDC-101, a mechanism that was further shown to be mediated by downregulation of survivin, an established mediator of radioresistance.[135–137] Significant further research is required before this can be added to the clinical treatment armamentarium; notwithstanding, the optimistic preliminary results highlight a potential modality for dose minimization, enhanced local control, and decreased morbidity.

Childhood irradiation for craniopharyngioma, particularly via EBRT, is well documented to carry a significant burden in terms of long-term functional consequences, including both the same major morbidities associated with surgical resection such as hypothalamic–pituitary access dysfunction, and other, radiation-specific complications including cognitive dysfunction, memory loss, optic neuropathy, vascular injury, radiation necrosis, and secondary neoplasms.[7] Endocrine dysfunction is especially problematic, with more than two-thirds of children developing growth hormone deficiency or hypothyroidism following craniopharyngioma irradiation.[99,108,138,139] Notwithstanding, the few analyses that have compared functional and quality-of-life outcomes have suggested that the overall morbidity of RT is substantially less impactful than the morbidity of GTR; correspondingly, in patients for whom aggressive resection would very likely result in severe hypothalamic or pituitary dysfunction, planned STR followed by an optimized RT plan may provide the best overall combination of minimized morbidity with maximized local control.[15,49–54]

Intracavitary Therapy: Aspiration, Brachytherapy, Bleomycin, and Interferon

Numerous strategies directed toward the cystic craniopharyngioma superstructures have been trialed, with varying degrees of success. Simple aspiration without introduction of a radionuclide or pharmacologic agent may provide minimal symptomatic relief, but is fundamentally a palliative technique, as cyst fluid is universally expected to reaccumulate.[140–142] Placement of an Ommaya reservoir provides persistent access for serial drainage interventions, but should not be considered a first-line treatment for primary disease, or even initial recurrences.

Introduction of β-emitting radionuclide suspensions including yttrium 90 and phosphorus 32 has been trialed, with variable success, ranging from complete-to-partial size reduction in 71% to 88%, cyst stabilization in 3% to 19%, and persistent growth in spite of therapy in 5% to 10%.[143–147] Treatment morbidity is similarly unpredictable, with worsening of visual deficits occurring in 6% to 58%, and new hormonal dysfunction occurring in 3% to 55%, moderately lower morbidity associated with ^{32}P as compared with ^{90}Y.[141,145,147] Across all modalities, improved efficacy is correlated with simpler cystic architecture—monocystic, thin-walled tumors demonstrate the best results—and treatment should be reserved for patients who are not expected to go on to further surgical resection, as scarring of the arachnoid is frequently observed, predisposing patients to a very high risk of hypothalamic injury at a subsequent dissection.[148–150]

Bleomycin is an antibiotic with antineoplastic properties that has been successfully used in the treatment of squamous cell carcinomas, where it disrupts DNA synthesis. Given the dysplastic squamous epithelium characteristic of craniopharyngioma cysts, intracavitary bleomycin has been trialed as another means of inducing cyst regression, with significant size reduction observed in 64% to 86% of patients, in small trials with sample sizes under 10.[151–154] In contrast to radionuclide infusion, bleomycin is considerably more dangerous if it extravasates, risking blindness, hypothalamic injury, ischemia, and even death; however, if successfully administered, it frequently results in smaller, thicker-walled cysts that are more amenable to resection.[155–158]

Intracavitary interferon-α, which is thought to restrict cyst growth by inducing Fas-mediated apoptosis, was trialed by Cavalheiro et al in a small study of 21 children, all of whom had at least a 60% reduction in net cyst volume.[159–162] In their report, 11 patients demonstrated greater than 90% volume reduction, 7 had 70% to 90% reduction, 3 had less than 70% reduction, and 2 progressed despite treatment. Side effects were minimal, with new endocrinopathies observed in only 15%, and another 30% developing minor complications such as weight loss, poor oral intake, fatigue, and behavioral abnormalities. A larger phase II clinical trial focused on unresectable or recurrent pediatric craniopharyngioma in patients both with and without prior radiation is underway, and will hopefully provide further insight into its definitive role in the armamentarium (NCT01964300). Perhaps surprisingly, at least three patients with robust responses had previously failed bleomycin, suggesting that interferon-α may present a safer and more efficacious intracavitary agent; however, long-term outcomes have not been reported, and only two patients went on to resection,

limiting insight into the potential impact of interferon-α on surrounding arachnoid planes.

Treatment of Recurrent Craniopharyngioma

Management of tumor recurrence is a challenging and nuanced issue, which demands significant individualization, based largely on the initial treatment strategy, and the anatomic extent of the recurrence. Many surgeons have described a dramatic increase in the difficulty of tumor dissection at repeat resection, including Professor Yasargil, attributable to the destruction of the arachnoid planes and subsequent formation of dense adhesions between residual tumor, hypothalamic tissue, surrounding vasculature, and the optic apparatus.[48,163–165] Consequently, a second operation is approached with marked trepidation, and should only be considered if RT has failed, unless an obvious, undissected trajectory is accessible—for example, a transsphenoidal approach to a limited intrasellar recurrence in a tumor that had initially been resected transcranially.

When a second resection is undertaken, the risk–benefit calculus regarding extent-of-resection is heightened exponentially. Although GTR has been associated with a significantly decreased risk of second recurrence and increased time-to-second-recurrence, STR is recommended in any circumstances where tumor is clearly adherent to neurovascular and hypothalamic structures, as reported outcomes in attempted repeat GTR have been guarded, with total tumor removal being achieved in just over half of patients, with perioperative mortality increasing several fold—from 3.7% to 13% in one multicenter study.[2,13,46,48,163,165] Where possible, planned STR at repeat surgery should target areas that progressed in spite of RT; if stable residual cannot safely be resected, the risk–benefit calculus typically favors leaving it in place.[166] Alternatives to repeat surgery include second RT modalities, such as SRS for a patient previously treated with adjuvant EBRT or CRT, intracavitary therapies as detailed above, and palliative cyst decompression.

Unfortunately, recurrence carries a significant decline in overall survival, whereas overall 10-year recurrence-free survival after GTR, STR with adjuvant RT, or RT all range from 77% to 100%, that drops to 29% to 70% following a recurrence.[45,144] Although some evidence suggests that young age at diagnosis or recurrence is protective, a shorter time-to-recurrence is predictive of a worse outcome in all age groups.[10,167,168] Similarly, morbidity is markedly increased following tumor recurrence, with at least 50% of patients incurring a significant, permanent decline in visual or hypothalamic–pituitary axis function following secondary treatment.[110,169,170]

The most insightful study of craniopharyngioma recurrence that underwent a relatively standardized, modern protocol of resection followed by adjuvant CRT documented 18 recurrences in a cohort of 97 children, as reported by Klimo et al[166] Of those 18 patients, 11 had multiple recurrences, leading to a total of 38 treatment interventions including craniotomy ($n = 27$), Ommaya placement for cyst drainage ($n = 6$) or intracavitary bleomycin ($n = 1$), transsphenoidal surgery ($n = 2$), and SRS ($n = 2$). Notable complications were observed in 9, and included DI, hyponatremic seizures, visual field deficit, lower cranial neuropathies attributable to bleomycin extravasation, and radiation-induced vasculitis; three deaths were observed, one in the immediate postoperative period most likely due to uncorrected preoperative endocrinopathy, and two attributable to sepsis unrelated to surgery or shunt infection. Interestingly, their overall 5- and 10-year survival rates in both the nonprogression and progression cohorts were appreciably higher than in preceding cohorts at 100%, 96%, 94%, and 88%, respectively. These results are encouraging that, in spite of the extraordinary challenges inherent to these tumors and their recurrences, the overall treatment trajectory has continued to improve, and that good outcomes can be achieved via a philosophy of maximal safe therapy followed by adjuvant RT, careful radiographic surveillance, and individually tailored treatment of recurrent or progressive residual tumor.

Complications and Their Management

Broadly, the complications of craniopharyngioma treatment fall into four major categories—pituitary, hypothalamic, visual, and general neurosurgical—though a few characteristic rarities do not fit that paradigm, most notably fusiform dilatation of the carotid artery (FDCA). Although efforts to establish an accurate and reproducible preoperative risk scoring system have been fraught with difficulty, most authors have observed consistently that tumor proximity to and investment in the hypothalamic–pituitary axis and visual apparatus are predictive of long-term disability.[46,51,99,171,172]

Pituitary dysfunction is all but ubiquitous after craniopharyngioma treatment: at least 25% of patients present with some degree of subclinical abnormality, and long-term dependence on pharmacologic replacement is expected in approximately three-of-four patients.[7,172] More specifically, both thyroid and growth hormone derangements are frequently observed, with 79% to 97% of patients requiring thyroid supplementation, and 70% to 93% requiring growth hormone replacement.[99,108,138,139] Pharmacologic treatments have been relatively successful in mitigating long-term consequences of the frequent postoperative growth hormone deficiencies, particularly in patients without hypothalamic involvement, who may reach normal adult height even without supplementation.[138,173] Of note, although several studies have demonstrated no association between supplemental growth hormone and tumor recurrence or progression of central nervous system tumors in general and craniopharyngiomas in particular, a small number of anecdotal cases have suggested the possibility that recurrences may rarely be stimulated or augmented by hormone administration.[174–179]

More prevalent and troublesome yet, DI is transiently observed in 80% to 100% of patients postoperatively, with a permanent syndrome persisting in 40% to 93%.[46,51,66,99,139,180,181] The clinical trajectory of acute DI can be challenging to predict, difficult to control, and in its most severe forms, potentially life-threatening. All patients require close postoperative sodium and fluid monitoring in an ICU setting, and should

be regarded with a high index of suspicion. If characteristic DI abnormalities appear, including high output of dilute urine (>300 mL/h, SG < 1.005), or acute hypernatremia (Na > 145), we recommend aggressive treatment with urine replacement using NaCl 0.45% and DDAVP (initial dose 2 μg SQ or 0.2 mg PO; repeat at 2 hours if response inadequate; max daily dose 4 μg SQ or 0.4 mg PO). In its more benign iterations, some patients normalize quickly, while others stabilizing into a chronic, euvolemic DI state, and rare individuals cycle through bi- or triphasic episodes of alternating polyuria and antidiuresis.[182–184]

Perhaps the most morbid long-term complication of craniopharyngioma treatment is hypothalamic dysfunction, which is manifest in many forms, including obesity-hyperphagia syndromes, sleep cycle disturbances, temperature dysregulation, and psychosocial dysfunction.[56,139,172] Although clinically detectable in ~35% of children at diagnosis, moderate-to-severe postoperative disability has been documented in as high as 65% to 80% of pediatric craniopharyngioma patients following treatment.[139,172,181] Obesity is the most common symptom, with up to 55% of children demonstrating significant weight gain within 6 to 12 months of treatment.[180,185] Secondary complications of obesity and disordered eating are often even more pronounced and debilitating, and may include metabolic syndrome, atherosclerosis, sudden cardiac death, psychosocial dysfunction, depression, multisystem disease, and increased all-cause mortality.[56,111,165,173,181,186–189]

As compared with pituitary dysfunction, hypothalamic injury is exceedingly difficult to manage, and available treatments are directed at mitigation of symptoms—such as bariatric surgery, antihyperlipidemics, and antihyperglycemics. No cause-directed therapies are available at present; however, several agents are under scrutiny in active clinical trials, including diazoxide with metformin, beloranib, exenatide, and intranasal oxytocin (NCT00892073, NCT02063295, NCT02860923, NCT02849743). Particularly with respect to the sequelae of hypothalamic injury, pediatric patients are at once more vulnerable, and more difficult to treat, suggesting that prevention via a hypothalamic-sparing surgical approach may be an ideal overall strategy—a tactic that, as discussed above in detail, has been shown to provide comparable local control, with significantly decreased hypothalamic morbidity and improved long-term quality-of-life.[54,55,190] Where indicated, the EEA may further optimize this balance between extent-of-resection and hypothalamic preservation, particularly as endoscopic technologies improve and surgical experience evolves; preliminary data are promising, but long-term outcome studies specifically comparing EEA and transcranial approaches to pediatric craniopharyngioma remain forthcoming at present.[70,72,191–193]

Like hypothalamic injuries, insults to the visual pathway have very limited treatment options, and are frequently cited by patients as the most significant contributor to poor long-term quality-of-life after craniopharyngioma resection.[56] A visual field defect or decreased visual acuity is a presenting symptom in approximately half of all pediatric patients, and is detectable on formal ophthalmologic examination in up to 80%.[48,194,195] Although postoperative improvement in visual symptoms is noted after primary surgery in 41% to 66% of patients, these gains are a qualified victory, as tumor recurrence and adjuvant RT are risk factors for the development of subsequent visual dysfunction.[13,46,48,56,66,165] In parallel, postoperative deterioration is a common surgical complication, occurring in 5% to 30% of resections, with some data suggesting a significantly lower rate after transsphenoidal resection—particularly in the EEA era.[48,65,70,71,192,196] As with hypothalamic dysfunction, injury prevention is ultimately a more potent strategy than treatment; however, excessive hedging during primary resection for fear of an insult to the visual pathway may come at a high cost, as the rates of injury following tumor recurrence and repeat treatment are substantially elevated.

General neurosurgical complications are diverse, and will be familiar to all cranial surgeons. Hydrocephalus is the most common and life-threatening treatable complication in this category, and can be managed according to routine protocols for CSF diversion and intracranial pressure management. Preoperative shunting is rarely required, but placement of an external ventricular drain at the beginning of the operation may provide useful relaxation in appropriately selected individuals. Cerebrovascular injuries are uncommon, but present an important source of permanent neurologic deficit following craniopharyngioma resection, particularly in the setting of recurrent disease, where the risk is especially elevated. Other less common treatment complications include cranial neuropathies, seizure disorders, and rare radiation-induced abnormalities ranging from secondary neoplasms to vasculopathy, iatrogenic moyamoya disease, and aneurysm formation.[49,109]

FDCA is a rarely reported but oft-discussed complication of radical craniopharyngioma resection, though Elliott et al suggest that this discrepancy is attributable in part to an underreporting phenomenon, with the true incidence theoretically approaching 10% to 20% in the pediatric population.[197] The phenomenon is hypothesized to follow from intraoperative retraction causing injury to the vasa vasorum of the supraclinoid internal carotid artery (ICA), resulting in chronic ischemia of the muscularis propria, and ultimately fusiform dilatation. RT has been suggested as a contributing factor in a minority of cases; however, FDCA is distinct from RT-induced aneurysms, both radiographically (the morphology is fusiform, not saccular), and with respect to the natural history (no FDCA rupture has been reported; all followed FDCA lesions have stabilized without intervention).[198–202] Although no primary treatment is required beyond radiographic observation, consideration should be given to SRS or a contralateral approach in the event of tumor recurrence, to avoid further insult to the presumptively weakened ICA.[42,112,203]

Conclusions

Management of pediatric craniopharyngioma is a neurosurgical Gordian knot, yet it is one that must continue to be painstakingly untied and unraveled, as our knowledge of the

disease's molecular underpinnings, optimal approaches, and clinical outcomes ultimately evolve into a dynamic treatment paradigm that can be tailored to each patient. Perhaps the most important lesson of pediatric craniopharyngioma is that our overall lack of true understanding is best reflected in the diversity of publications describing a staggering array of often-equivocal treatment protocols. Our present strategy reflects the insights of our many diverse predecessors: where possible, we advocate safe, maximal, hypothalamic-sparing resection as the initial treatment, with EEA, intraventricular, and transcranial skull base techniques employed alone or in combination, as required by the tumor location and extension. Postoperative care involves close clinical and radiographic follow-up, with RT administered at the time of progression or recurrence—typically via IMRT, PBRT, or SRS, depending on the patient age, disease architecture, and extent of recurrence. Beyond that, attempts to systematize care are at the mercy of a protean disease, and our chief tactics are reduced to an individualized assault. Much remains unknown about these benign but highly morbid tumors, and correspondingly, the major treatment paradigms will continue to remain in flux, as we painstakingly advance the frontier—be it via the first suggestions of targeted therapies, new intracavitary treatments presenting promising results, the continued technological momentum and surgical expertise empowering EEA to take on more expansive lesions, or other exciting areas of potential discovery in pediatric craniopharyngioma.

Previous Presentations
None.

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