Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2022**; 27(12): 328
https://doi.org/10.31083/j.fbl2712328

Review

Current Approaches to Craniopharyngioma Management

Michael Joseph Diaz[1], Sean H. Kwak[1], Kevin Thomas Root[1], Angela Fadil[1], Andrew Nguyen[1], Lauren Ladehoff[2], Sai Batchu[3], Brandon Lucke-Wold[4,*]

[1]College of Medicine, University of Florida, Gainesville, FL 32611, USA
[2]Morsani College of Medicine, University of South Florida, Tampa, FL 33620, USA
[3]Cooper Medical School, Rowan University, Camden, NJ 08103, USA
[4]Department of Neurosurgery, University of Florida, Gainesville, FL 32611, USA
*Correspondence: Brandon.Lucke-Wold@neurosurgery.ufl.edu (Brandon Lucke-Wold)
Academic Editor: Amancio Carnero Moya
Submitted: 18 October 2022 Revised: 6 December 2022 Accepted: 13 December 2022 Published: 21 December 2022

Abstract

Craniopharyngiomas (CP) are rare noncancerous brain tumors located in the skull base. To date, CP remain challenging-to-resect tumors, owing to their difficult location and invasive potential, with profound adverse effects for the patient if left to grow. Indeed, gross total resection may also be accompanied by unwelcome sequalae, underscoring the need for continued investigation. In the present work, we provide a scoping review of current CP management, with emphasis on our knowledge of their genesis, available treatment options, post-intervention clinical outcomes. Leading theories of CP development are (1) the embryonic theory, explaining the development of adamantinomatous CP from epithelial remnants of Rathke's pouch and (2) the metaplastic theory, which describes papillary CP development as a result of adenohypophyseal cell metaplasia. Treatment may include surgery, intracystic therapy, or irradiation depending on tumor size, history and location. However, whether a single ideal approach and timing for CP intervention exists remains debated. We appraise and critique these areas with priority for emerging basic results and innovation.

Keywords: craniopharyngioma; skull base cancer; current management; benign tumor; literature review

1. Introduction

Craniopharyngiomas (CP) are benign tumors derived from cell remnants of the Rathke's pouch and are further classified as adamantinomatous type or squamous papillary type [1,2]. CP are a rare intracranial tumor in adults; however, they account for up to 10% of such tumors in children [3]. In an epidemiologic study using the Central Brain Tumor Registry of the United States, Momin *et al.* [4] found an incidence rate of 0.16 confirmed cases per 100,000 persons. They observed a bimodal distribution of incidence with a peak at 5 to 9-year-olds and another at 55 to 69-year-olds. When stratifying by race/ethnicity, they found the highest incidence rate in blacks, followed by whites [4]. Furthermore, black ethnicity was associated with a decreased survival rate [4]. These findings agreed with previous literature where Zacharia *et al.* [5] identified 644 patients with CP and determined that black ethnicity was an age-adjusted relative risk for craniopharyngioma compared with white ethnicity [4]. Additionally, Momin *et al.* [4] confirmed that adamantinomatous craniopharyngiomas were significantly more common in populations of all ages when compared to papillary tumors.

The diagnosis of childhood-onset craniopharyngiomas is often made several years after the first manifestation of symptoms—indeed, many are detected incidentally [6]. Some of the reasons for its incidental identification are imaging prompted by cerebral palsy, nasal obstruction, or head trauma. Conversely, CP found due to direct symptoms often presented with increased intracranial pressure manifesting as headache or nausea in addition to symptoms of growth retardation and visual impairment [7]. Furthermore, at the time of diagnosis, approximately half of all patients presented with one or more endocrine defects [8]. In a retrospective review of 107 craniopharyngioma patients, Capatina *et al.* [9] determined that children were more likely to exhibit symptoms of nausea/vomiting, photophobia, diabetes insipidus, or growth hormone deficiency when compared to adult patients. Additionally, in a retrospective analysis of patient records with a prospective longitudinal follow-up, Hoffmann *et al.* [6] found that the average duration of symptoms in children before diagnosis was 6 months. Namely, CP was frequently diagnosed after a longer history of symptoms in older children compared to younger children. Adults with craniopharyngiomas present similarly with endocrine disorders, specifically hypothyroidism-related symptoms. However, Capatina and colleagues [9] reported impaired visual acuity or impaired visual fields to be more frequent in adult patients.

The adamantinomatous craniopharyngioma (ACP) subtype is precipitated by a somatic mutation in CTNNB1 which encodes the protein β-cantein [10,11]. Point mutations of the protein influence its stability, leading to decreased degradation and accumulation within the cell [12]. Furthermore, Hölsken *et al.* [12] found this mutation and aggregation of β-cantein to lead to overactivation of the

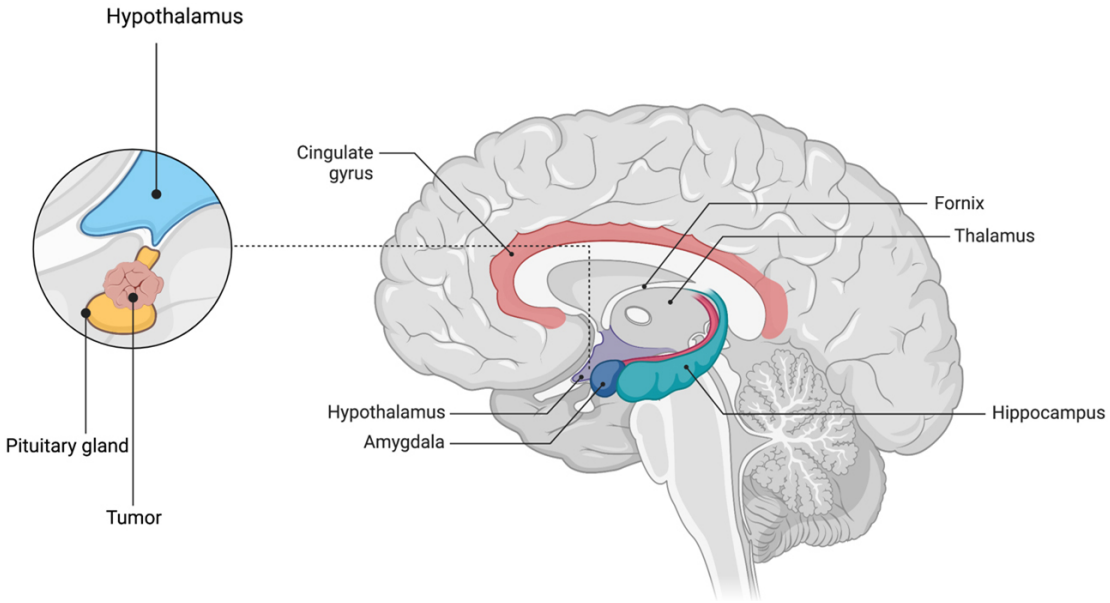

Fig. 1. Craniopharyngiomas often develop near the pituitary glands and hypothalamus along the glandular tissue of the pars tuberalis covering the pituitary stalk. Figure created with Biorender.com™.

WNT pathway which has a causative role in the genesis of craniopharyngioma [13]. Papillary craniopharyngiomas (PCP) are linked to mutations of BRAF-V600E. Therefore, while the crucial pathogenic event in ACP is activation of WNT, in PCP it is activation of the Ras/Raf/MEK/ERK pathway via BRAF V600E mutation [14]. In a SEER (Surveillance, Epidemiology, and End Results database) Population-Based Analysis, Teng *et al*. [15] found the overall survival curves at 3, 5, and 10 years to be 89.1%, 86.2%, and 83%, respectively. Furthermore, they found that age, ethnicity, tumor size, and radiation therapy were predictive of overall survival at initial diagnosis with younger age, decreased tumor size, white ethnicity, and radiation therapy to be associated with significantly better survival [15].

The onus is upon the treating physician to familiarize themselves with the current literature of craniopharyngiomas to improve patient outcomes. Therefore, we aim to discuss current theories of development as well as treatment options including surgical techniques, intracystic therapy, radiotherapy, and clinical outcomes in the present review of English studies published in PubMed/MEDLINE from inception to date.

2. Theories of Development

2.1 The Embryonic Theory

The most common subtype of craniopharyngiomas is the adamantinomatous craniopharyngioma (ACP), which is found in both children and adults. The embryonic theory is used to explain the development of ACP [16–18]. During embryogenesis, an ectodermic pouch called Rathke's diverticulum is formed in the bucco-pharyngeal membrane, from which the anterior pituitary gland develops. This outpouching then invaginates and ascends upward between the forebrain and hindbrain of the embryo, becoming Rathke's pouch. The cells of Rathke's pouch proliferate rapidly during the 5th week of gestation, elongating cranially while remaining transitorily connected to the roof of the embryonic oral cavity by the pharyngo-hypophyseal stalk. This extension of Rathke's pouch, termed the craniopharyngeal duct, later involutes during the 7th week of gestation [19]. In certain instances, the craniopharyngeal duct fails to involute completely and remnants of these ectodermal cells may remain and give rise to a craniopharyngioma [16,19,20]. It is postulated that craniopharyngiomas may originate at any position along the tract of migration of Rathke's pouch [17,18,21,22], thus providing an explanation for the development of craniopharyngiomas at both intrasellar and suprasellar locations. Additionally, ACP are believed to form due to somatic mutations in CTNNB1 during embryogenesis [19], leading to excessive β-catenin protein production and eventual tumor growth and development.

2.2 The Metaplastic Theory

The metaplastic theory is commonly used to describe the development of papillary craniopharyngioma (PCP), which are primarily found in adults. PCPs arise from metaplasia of the adenohypophyseal cells within the pituitary gland and result in the formation of differentiated squamous cell nets [19,23]. Though craniopharyngiomas formed via metaplasia also arise in a similar location as those of embryological origin, support for the metaplastic theory arises due to the identification of epithelial cell nests in healthy adult pituitary glands along the glandular tissue of the pars tuberalis covering the pituitary stalk [22,23] (Fig. 1). These epithelial nets typically occur with increasing patient age,

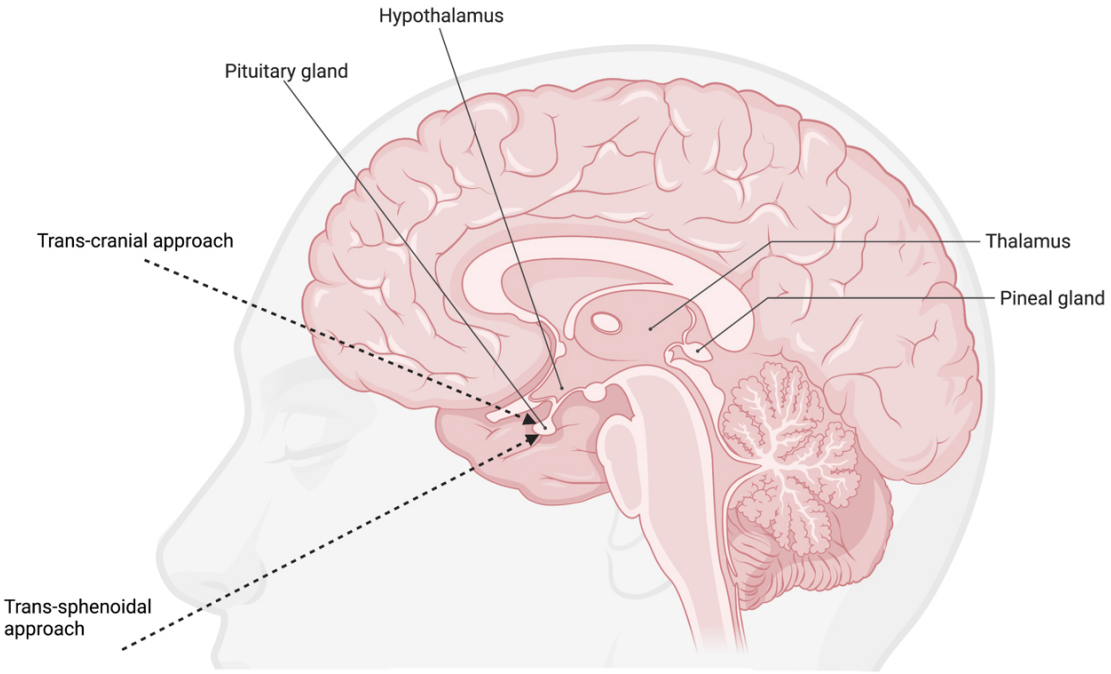

Fig. 2. An illustration of the Trans-cranial and Tran-sphenoid surgical approaches of craniopharyngioma resection. Figure made with Biorender.com™.

which may also be why PCPs primarily occur in the adult population. Moreover, PCPs commonly develop due to somatic BRAF mutations [19], which are commonly upregulated in different types of cancer due to increased activation of the MAPK pathway.

2.3 Surgery

Craniopharyngiomas are rare, WHO Grade 1 tumors of the central nervous system nested near the pituitary gland and typically accompanied by neuroendocrine dysfunction. Their proximity to vital neurovascular structures (namely the optic chiasm and the hypothalamus) most commonly indicates microsurgical intervention for safe removal.

2.4 Transcranial Surgery

Transcranial surgery (TCS) is a type of craniotomy involving the opening of cranial bone flaps which has been long relied on for resection of large tumors located in challenging areas (e.g., the skull base). TCS offers several possible entry points for CP resection: transsphenoidal, interhemispheric, unilateral subfrontal/bifrontal transbasal, pterional-frontotemporal, modified orbitozygomatic, and posterior transpetrosal approaches [24]. At the time of writing, TCS remains the preferred approach for suprasellar CP and large intra-suprasellar CP featuring hypothalamic and third ventricle invasion [25] (Fig. 2). Pooled effects analysis observed favorable post-operative visual and endocrine outcomes among patients receiving TCS, compared to new-age endonasal endoscopic techniques (p-value = 0.038, p-value = 0.016, N = 3079) [26]. However, transcranial approaches are not without limitation. TCS realized with higher rates of CP tumor recurrence [27] and higher frequency of severe adverse events, including perioperative death, when compared to transsphenoidal entry [28]. Yet, transcranial surgery remains the preferred surgical option for CP located above the sella turcica as well as CP extending towards the hypothalamus and/or third ventricle [25].

2.5 Standard and Extended Transsphenoidal Approaches

TSS and extended TSS (eTSS) are well-established microsurgical options for endoscopic removal of intra- and para-sellar tumors, respectively, through the sphenoid sinus. Transsphenoidal entry is especially indicated for intrasellar CP in patients with enlargement of the sella turcica floor [29]. Success rates of total CP resection by TSS and eTSS are largely positive in general population: Yamada *et al.* [30] reported complete tumor removal in 77.8% (70/90) of patients in an adult-pediatric mixed cohort; Kitano *et al.* [31] reported complete tumor removal in 86% (19/22) of patients in an adult-pediatric mixed cohort. However, while transsphenoidal approaches are effective for CP resection, post-operative hypopituitarism is also not uncommon and frequently manifests in new-onset diabetes insipidus [30–32]. There too exists data suggesting that CSF leakage is more probable among patients with CP that were treated with [31,33,34]. Recent research has also indicated advancement in the form of eTSS variants, which may afford enhanced tumor access of CP for which TCS is traditionally indicated, albeit with variable success. In 2007, Laufer *et al.* [35] first described the utility of a purely endoscopic endonasal approach for minimally invasive resection of. Surgical evidence has only since supported this

technique for retrochiasmatic CP, citing excellent midline access and visual improvements without an increased risk profile compared to convention [36,37]. The smattering of recent evidence suggesting new utilities of TSS/eTSS for CP should continue to excite the greater neurosurgical community, particularly in the surgery of complicated skull base tumors.

Evaluating intracystic therapies in the context of increasingly refined surgical approaches also warrants consideration. Currently, the aforementioned therapies are deferred to over surgery primarily in the context of unique situations—namely, pediatric populations that impose limitations on the effectiveness of surgery [38]. For example, physical limitations for the endoscopic endonasal approach include narrow anatomical borders within the nasal region. Ideally the choice of approach is based on CP topography and anatomical features of the patient. In a retrospective review of 315 patients, Fan and colleagues [39] compare endoscopic endonasal and transcranial approaches, particularly highlighting the heterogenous nature of CPs. Their results convey CP topography (differentiating three categories: infrasellar/subdiaphragmatic, subarachnoidal, and pars tuberalis CPs) advantages for the endoscopic endonasal approach in that endonasally treated patients displayed higher rates of visual improvement and CSF leaks overall. Regarding par tuberalis CPs, endonasal procedures were associated with longer operative durations, higher gross-total resections, and decreased recurrence rates [39]. Cao *et al*. [40] analyzes 22 cases to determine such efficacy with the following observations: gross total resection was attained in over 95% of the cases (n = 21), with 68% (n = 15) developing new onset endocrinological deficits. Barring these complications, the endonasal approach is suggested to perhaps be useful for resection of IVCs without significant morbidities or lethality [40]. In a similar vein, Kassam and colleagues [41] also touch on the heterogenous considerations CPs demand based on the regional locations of their parasellar extensions. They describe a four-type classification scheme elaborating on the types which contraindicate an endonasal approach (IV), further highlighting the topological heterogeneity of CPs [41].

3. Intracystic Therapy

3.1 Intracavitary Radiation

Beta-gamma radiation remains the most established and well understood of the intracystic treatment options in craniopharyngiomas. This therapy is most effective for postoperative resection as a means of supplementing size maintenance or for incomplete tumor resections. It is implemented with the use of beta-emitting radioisotopes, commonly phosphorus^{32}, aurum^{79}, rhenium^{75}, or yttrium^{39} [42,43]. These isotopes are typically introduced via a multifunctional catheter device, namely the Ommaya reservoir device, allowing for precise aspiration of cerebrospinal fluid (CSF) proceeded by administration of radioactive substance. Isotopic dose often ranges from 200–400 Gy, else potential complications may arise, dependent on multiple considerations, especially the estimated cyst size measured from the volume of CSF aspirated [43]. The primary drawback of intracystic radiation therapy comes from the scarcity of available facilities housing the resources and isotopes required to undergo such therapy. Clinical drawbacks include induction of secondary tumors, off-target radiotoxic damage to surrounding structures, and delayed onset of vasculopathies, moyamoya disease in particular [8,44]. Nonetheless, several instances of success have been reported in the form of cyst volume reduction spanning 80–100% of cases, across multiple case series studies [8,45].

3.2 Bleomycin and Interferon alpha, a cytokine (IFN-alpha)

Another potential route of treatment has been explored in the form of pharmaceutics. Bleomycin is the most common drug used for volume control in craniopharyngioma patients. Unlike radiation therapy, it is not effective as a means of long-term remission maintenance [45]. Regardless, its mitigated risk relative to radiation has led to its favor in extenuating circumstances, or situations that benefit from short delays such as pediatric populations which may be particularly vulnerable to radiation exposure. Bleomycin is a polypeptide antibiotic (bleomycin A2 and B2) secreted by Streptomyces verticillus inhibiting RNA and DNA synthesis, particularly effective in skin cancer [46]. Its use in craniopharyngiomas was first reported in 1985 by Takahashi and colleagues [46,47]. Similarly, to radiotherapy, bleomycin is administered with a catheter and Ommaya reservoir often with stereotactic guidance. Reported doses have ranged from 1 to 15 mg, with $\geq$5 mg seen in larger cysts. In a case series of 17 children, all had undergone a 50% reduction in volume when undergoing primary bleomycin treatment [48].

As another drug, IFN-alpha has been viewed as an alternative to bleomycin for its likewise antitumoral properties, though in the form of cytokine secretion and T-cell activation [49]. The most important advantage of IFN-alpha is its relative absence of neurotoxic complications. Bleomycin is not unlike radiation in its potential for severe consequences, which include, but are not limited to peritumoral edema, cerebral infarcts, and death [43,48,50]. IFN-alpha in its first reported use by Cavalheiro *et al*. [51] observed a reduction in cyst size in all 21 patients, reaching up to 90% reduction in 11 of those patients. Since 2005, other groups have reported moderate success in cystic CP treatment with IFN-alpha Between the three therapies, the prevailing sentiment is that surgical resection is the most effective means of treating craniopharyngiomas [52,53]. Overall, alternative modalities such as these may be more viable in extenuating circumstances, those requiring delay, or situations benefiting from combination therapy with resection.

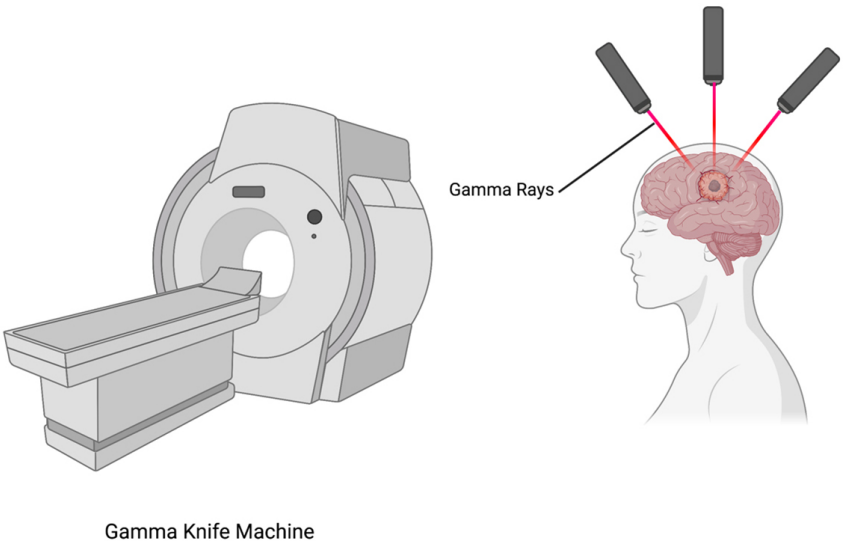

Fig. 3. A depiction of a stereotactic radiosurgery which can be used in the treatment of craniopharyngioma patients. Figure made with Biorender.com™.

4. Radiotherapy

4.1 External Beam Radiation Therapy

Radiotherapy in combination with surgery remains the mainstay of the multi-disciplinary and highly individualized treatment required for the management of craniopharyngiomas [54]. Currently, the most common treatment strategy is a conservative subtotal resection followed by radiotherapy, with a focus on minimizing treatment-related toxicities [55]. Although a cure may be possible with gross total resection, subtotal resection followed by radiation is generally considered a safer option, especially in children with hypothalamic invasion [38]. Several radiotherapy modalities exist in the treatment of craniopharyngioma given its highly heterogeneous nature that necessitates an equally individualized treatment planning. Three-dimensional conformal radiotherapy (3DCRT), which delivers a homogenous dose to the whole tumor, is the method of treatment for most clinical cases of craniopharyngioma [56]. Intensity-modulated photon radiotherapy (IMRT) is a form of 3DCRT that changes the strength of beams in certain areas, allowing stronger doses in particular tumor areas while lessening the damage to nearby normal tissues. In select cases, IMRT can improve dose conformality and reduce dosage to adjacent structures compared to 3DCRT [55]. A major advance in radiotherapy has been the introduction of imaging during treatment, ensuring that the tumor is targeted accurately throughout the course of treatment. This is particularly important in craniopharyngioma as many patients have a cystic component that can enlarge during radiotherapy. Image guidance radiotherapy (IGRT), such as Novalis or cone beam computed tomography (CT), enables the assessment of cystic growth and appropriate re-targeting of the tumor throughout the course of treatment.

4.2 Proton Beam Therapy

Proton beam therapy channels beams of protons that travel through the tissue like photon beams. The theoretical advantage of proton beam therapy over photon therapy is that protons deposit energy at a defined point along their path, reducing the harmful effects on normal tissues in front of and behind the tumor. Given this theoretical advantage, proton beam therapy is often utilized in pediatric craniopharyngiomas where any potential avoidance of normal tissue irradiation is deemed significant. In a retrospective review of pediatric patients with craniopharyngioma, proton therapy demonstrated excellent tumor control with minimal acute toxicity, yet late toxicities from the tumor, surgery, and radiation remain prevalent [57]. Dosimetric evaluation of 3D conformal proton therapy in pediatric craniopharyngiomas has demonstrated a reduction in irradiated brain volume, yet without improved target dose distribution compared to photon radiotherapy [58,59]. Proton therapy has also shown improved outcomes in preserving IQ scores [60] and academic achievement scores [61] compared to photon therapy in craniopharyngioma patients. In 2016, a newer generation of proton therapy (pencil-beam scanning) was introduced with the advantage of using small, individually weighted beams to better conform to the prescription dose and reduce the volume receiving the highest doses [1], yet the current literature on its long-term efficacy and toxicity remains limited.

4.3 Stereotactic Radiosurgery

Stereotactic radiosurgery (e.g., gamma knife), which delivers a single large dose of radiation to the target from multiple angles, may be an alternative to fractionated treatments in craniopharyngioma patients with smaller lesions [54] (Fig. 3). Single radiation doses above 8–10 Gy to the

optic chiasm have been associated with up to 25% risk of optic neuropathy, limiting this technique away from the optic chiasm [62]. Case series that confine stereotactic radiosurgery to smaller lesions report minimal morbidity [63–66] and rates of visual deterioration of 3% [64]. However, studies have shown worse outcomes regarding tumor control, questioning its utility as stereotactic radiosurgery is suitable primarily for smaller lesions away from critical brain structures [56]. As a major advancement to the conventional stereotactic radiosurgery, robotic mounted linac (e.g., cyberknife) has been introduced to deliver hypofractionated stereotactic radiotherapy usually across 2–5 fractions. Several studies on the clinical outcome and prognosis of craniopharyngioma patients who underwent cyberknife treatment reported effective tumor growth control with minimal adverse effects [66–68].

4.4 Brachytherapy

Brachytherapy involves implanting radioactive material inside the body and has been indicated as an alternative for treating cystic craniopharyngiomas. In a recent systematic review and meta-analysis, radioisotope brachytherapy in treating predominant monocystic or multicystic craniopharyngiomas showed effective tumor control and minimal morbidity, especially in the pediatric population [69]. Several reports have demonstrated that intracavitary brachytherapy irradiation with β-emitting sources such as phosphorus-32 (P-32) or yttrium-90 can be successful in treating cystic craniopharyngiomas while minimizing morbidities [70,71]. Studies also reported P-32 as a favorable β-emitting source due to its short range of tissue penetrance and steep dosage decline [72,73]. A large study on the long-term clinical outcomes of 90 patients with cystic craniopharyngiomas who underwent P-32-based brachytherapy reported progression-free survival rates at 5 and 10 years of 95.5% and 84.4%, respectively [74].

4.5 Clinical Outcomes

Both CP and its treatment can result in long-term sequelae that include endocrinopathy, hypothalamic dysfunction, and visual field defects [75]. Given CP location approximate to the pituitary gland, hypopituitarism is a common complication caused by tumor extension or iatrogenic structural damage [75,76]. In patients with endocrinopathy secondary to the tumor itself, Karavitaki *et al.* [77] found that tumor resection did not reverse hormonal deficits. One study found the 98% of CP patients have long-term pituitary hormone deficiencies [78]. Among the pituitary endocrinopathies associated with CP, growth hormone deficiency is the most common, although this is not often a cause for initial presentation [79]. Pediatric patients most often receive initial evaluation for delayed puberty related to gonadotropin deficiency [80]. In both children and adults, the side effects of hypopituitarism can precipitate low self-esteem related to physical appearance. Previously conducted quality of life (QoL) studies have identified lower rates of sexual activity and increased psychosocial dysfunction among adult patients treated for CP during childhood [81,82]. Hypothalamic damage also correlates with decreased psychosocial function due to consequent hyperphagia and obesity [83]. Further effects of hypothalamic lesions include deficits in memory, attention, and executive function [84]. QoL is further deteriorated by the high incidence of visual defects, which have been reported in 50% of children at initial presentation [85]. In a mixed cohort of pediatric and adult patients, the probability of visual disturbances at ten-year follow-up was 48% [77]. Additionally, CP patients have an increased risk of cardiovascular mortality, especially among women [86].

Although CPs are benign tumors, their prognosis is variable. Studies with mixed pediatric and adult CP cohorts demonstrated five-year survival rates of 54–96% [77,87] and ten-year survival rates of 40–93% [77,87,88]. Pediatric cohorts displayed five-year survival rates of 83–96% [89] and ten-year survival rates of 65–100% [90,91]. Average twenty-year pediatric survival was reported at 62% [1]. Additionally, long-term outcomes are marked by substantial morbidity. Reported CP recurrence rates range from 17–40% [28,92–97]. Median time of first recurrence ranges from 30 to 45 months [77,97]. Among patients with tumor recurrences, local recurrence is most common, although there are documented instances of ectopic CPs due to iatrogenic seeding of the surgical tract and cerebrospinal fluid [98]. Regarding therapeutic approach, a recent meta-analysis observed no statistically significant difference in recurrence rates between adult CP patients treated with gross-total resection and those treated with incomplete resection and radiotherapy [94]. Similarly, pediatric populations experience high recurrence rates despite complete tumor excision [99]. Given the frequency of recurrence regardless of treatment modality, attention has turned to quality of life (QoL) outcomes [99]. The recent advances in CP therapy have lower risks of surrounding structural damage [100]. Therefore, the treatment paradigm has shifted away from gross total resection in favor of conservative approaches with less associated morbidity [1]. Among these approaches also includes focused ultrasound, which has demonstrated promise in disrupting the blood-brain barrier, inciting increased immune cell infiltration and slowed proliferation of other brain tumors [101,102]. However, generalized clinical outcomes cannot properly assess the individual CP prognosis after employing a specific surgical/radiotherapy treatment. Given their significant topographical and pathological heterogeneity, selecting the optimal approach to CP therapy relies on an accurate characterization of the tumor.

5. Pathological Variables Influencing Management Outcome

5.1 Hypothalamic Involvement

In 2005, Sainte-Rose *et al.* [103] determined that CPs with no hypothalamic involvement (Type 0) are strong candidates for total resection. Similarly, those with hypothalamic compression without invasion (Type 1) can be totally resected with minimal exacerbation of morbidity. However, Hy-CPs (Type 2) warrant conservative treatment to maximize quality of life and prevent post-operative hypothalamic dysfunction. The classification system presented by De Vile *et al.* [104] evaluates post-operative hypothalamic damage on MRI based on the integrity of the third ventricle floor. In this schema, the ventricular floor may be intact (Grade 0), partially breeched (Grade 1), or entirely deficient (Grade 2). In 2007, Puget *et al.* [105] developed an updated multimodal classification system for hypothalamic involvement in pediatric craniopharyngiomas that utilizes De Vile's approach in conjunction with clinical presentation. Type 2 and Grade 2 CPs strongly correlate with the sequelae of hypothalamic dysfunction [1], supporting the current treatment paradigm of subtotal resection with radiotherapy for Hy-CPs [38]. However, even with conservative management, hypothalamic dysfunction may still occur. Preservation of function depends on the degree of hypothalamic involvement, which correlates with the CP origin [106]. Central-type CPs, which are found within and along the pituitary stalk with no visible origin, typically exhibit either mild (25.6%) or severe bilateral (53%) hypothalamic involvement. Although not all central-type CPs invade the hypothalamus (7%). CPs originating in the hypothalamic stalk invade the hypothalamus (100%) in a predominately severe and unilateral manner (52%). On the contrary, suprasellar stalk (20%) and intrasellar stalk (9%) CPs rarely invade the hypothalamus, and those that do exhibit only mild involvement. The summative value of this information provides physicians with multiple tools to assess for potential hypothalamic involvement and modify the treatment course accordingly [107].

5.2 Topographical Variants

Functional outcomes and recurrence rates in CP are influenced by tumor location. Since 1990, three topographical presentation systems have been presented. Yaşargil *et al.* [108] introduced the first system based on surrounding anatomical structures. The optimal surgical approach depended on the type of CP according to this classification schema. However, endoscopic advances in the early 2000s prompted Kassam *et al.* [41] to devise a new classification system: pre-infundibular (Type I), trans-infundibular (Type II), and purely intraventricular (Type IV). This scale was later expanded by Jamshidi *et al.* [109] to include subdiaphragmatic tumors (Type 0) that can be resected via standard transsphenoidal approach. Most recently, Pan *et al.* [110] proposed a novel CP classification system known as "QST": infrasellar/subdiaphragmatic tumors (Q-CPs), subarachnoidal CPs (S-CPs), and pars tuberalis CPs (T-CPs). In a small cohort study, patients with T-CPs were found to have a statistically significant poorer prognosis than patients with Q or S-CPs [111]. However, larger studies may be required to further evaluate prognostic differences based on QST classification. Still, the QST classification system has utility in determining CP growth pattern and, therefore, optimal surgical approach [112]. Additional methods of CP topographical classification include structures attached to the tumor, adhesion morphology, and adhesion strength [113]. Using these factors, Prieto *et al.* [114] devised a risk stratification model that predicts surgical outcome. In the study, increasing degrees of adhesion positively correlated with worsening post-operative outcomes. Additionally, greater degrees of adhesion demonstrated poor overall clinical outcomes. CP topography was the greatest predictor of adherence severity, with the strongest degrees of adherence found in suprasellar-pseudointraventricular, infundibulo-tuberal, and secondary intraventricular CPs. In addition to hypothalamic invasion, severe tumor adhesion may represent a limitation of gross total resection.

More recently, findings related to topographical and pathological heterogeneity have allowed pre-sight into clinical outcomes and management of care. Earlier this year, Pascual and colleagues conducted a systematic review of 5085 CP cases characterizing a duct like diverticulum (DV) or a narrow, hollow tubular structure of the papillary CP type [115]. Significantly, the DV sign was identified to be pathognomonic for papillary CP type with 100% specificity while also establishing a confined, intra-3rd-ventricle (3VF) location of the subtype with a 95% specificity among adult patients [115]. This pathological and topographical information is invaluable information for a neurosurgeon when planning surgical resection or targeted therapy [115]. This claim is further evidenced by recent demonstrations of total resection of the CP subtype, illustrating the use these findings [40,116].

5.3 Concluding Remarks

Here we addressed the relevant body of literature on present-day CP management and outcomes. Discussed topics include supported theories of development, practiced and researched treatment options, and expected pre- and post-operative clinical course. The available literature on surgical invention for CP suggests that endoscopic endonasal (or transsphenoidal) approaches may provide enhanced visualization and positioning for bimanual resection of challenging tumors, resulting in favorable clinical prognoses compared to conventional transcranial interventions. Brachytherapy and intracystic therapy have enjoyed some attention as alternative, but combined surgery and conventional external beam radiation therapy remain king for most all CP at the time of writing. Primary limitations of the present review were the sole utilization of MED-

LINE/PubMed for article selection and restriction to studies published in English. Nonetheless, we maintain that the findings shared here provide a coherent overview of what is currently understood of craniopharyngioma management and inform future research direction for clinicians and scientists alike.

Author Contributions

MJD and BLW conceptualized and coordinated this review. MJD, SHK, KTR, AF, AN, LL, and SB wrote the original manuscript. MJD, SHK, KTR, AF, AN, and BLW contributed to manuscript editing plus revisions. All authors approved of the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Müller HL, Merchant TE, Warmuth-Metz M, Martinez-Barbera J, Puget S. Craniopharyngioma. Nature Reviews Disease Primers. 2019; 5: 75.

[2] Garnett MR, Puget S, Grill J, Sainte-Rose C. Craniopharyngioma. Orphanet Journal of Rare Diseases. 2007; 2: 18.

[3] Bunin GR, Surawicz TS, Witman PA, Preston-Martin S, Davis F, Bruner JM. The descriptive epidemiology of craniopharyngioma. Neurosurgical Focus. 1997; 3: e1.

[4] Momin AA, Recinos MA, Cioffi G, Patil N, Soni P, Almeida JP, *et al*. Descriptive epidemiology of craniopharyngiomas in the United States. Pituitary. 2021; 24: 517–522.

[5] Zacharia BE, Bruce SS, Goldstein H, Malone HR, Neugut AI, Bruce JN. Incidence, treatment and survival of patients with craniopharyngioma in the surveillance, epidemiology and end results program. Neuro-oncology. 2012; 14: 1070–1078.

[6] Hoffmann A, Boekhoff S, Gebhardt U, Sterkenburg AS, Daubenbüchel AMM, Eveslage M, *et al*. History before diagnosis in childhood craniopharyngioma: associations with initial presentation and long-term prognosis. European Journal of Endocrinology. 2015; 173: 853–862.

[7] Boekhoff S, Bison B, Eveslage M, Sowithayasakul P, Müller HL. Craniopharyngiomas presenting as incidentalomas: results of KRANIOPHARYNGEOM 2007. Pituitary. 2019; 22: 532–541.

[8] Caldarelli M, Massimi L, Tamburrini G, Cappa M, Di Rocco C. Long-term results of the surgical treatment of craniopharyngioma: the experience at the Policlinico Gemelli, Catholic University, Rome. Child's Nervous System. 2005; 21: 747–757.

[9] Capatina C, Vintila M, Gherlan I, Dumitrașcu A, Caragheorgheopol A, Procopiuc C, *et al*. Craniopharyngioma - clinical and therapeutic outcome data in a mixed cohort of adult and paediatric cases. Acta endocrinologica. 2018; 14: 549–555.

[10] Buslei R, Nolde M, Hofmann B, Meissner S, Eyupoglu IY, Siebzehnrübl F, *et al*. Common mutations of beta-catenin in adamantinomatous craniopharyngiomas but not in other tumours originating from the sellar region. Acta Neuropathologica. 2005; 109: 589–597.

[11] Sekine S, Shibata T, Kokubu A, Morishita Y, Noguchi M, Nakanishi Y, *et al*. Craniopharyngiomas of adamantinomatous type harbor beta-catenin gene mutations. The American Journal of Pathology. 2002; 161: 1997–2001.

[12] Hölsken A, Buchfelder M, Fahlbusch R, Blümcke I, Buslei R. Tumour cell migration in adamantinomatous craniopharyngiomas is promoted by activated Wnt-signalling. Acta Neuropathologica. 2010; 119: 631–639.

[13] Gaston-Massuet C, Andoniadou CL, Signore M, Jayakody SA, Charolidi N, Kyeyune R, *et al*. Increased Wingless (Wnt) signaling in pituitary progenitor/stem cells gives rise to pituitary tumors in mice and humans. Proceedings of the National Academy of Sciences of the United States of America. 2011; 108: 11482–11487.

[14] Goschzik T, Gessi M, Dreschmann V, Gebhardt U, Wang L, Yamaguchi S, *et al*. Genomic Alterations of Adamantinomatous and Papillary Craniopharyngioma. Journal of Neuropathology and Experimental Neurology. 2017; 76: 126–134.

[15] Teng H, Liu Z, Yan O, He W, Jie D, Qie Y, *et al*. Nomograms for Predicting Overall Survival Among Patients with Craniopharyngiomas at Initial Diagnosis: A SEER Population-Based Analysis. International Journal of General Medicine. 2021; 14: 3517–3527.

[16] Senthilvel HNP, Krishnan SS, Vasudevan MC. Extracranial infrasellar craniopharyngioma. Neurology India. 2014; 62: 100–103.

[17] 2022 WHO classification of Tumours, 5th edition: Central Nervous System Tumors International Agency for Research of Cancer: Lyon. 2021.

[18] Wang EW, Zanation AM, Gardner PA, Schwartz TH, Eloy JA, Adappa ND, *et al*. ICAR: endoscopic skull-base surgery. International Forum of Allergy & Rhinology. 2019; 9: S145–S365.

[19] Ortiz Torres M, Shafiq I, Mesfin FB. Craniopharyngioma. In: StatPearls. StatPearls Publishing: Treasure Island. 2022.

[20] Müller HL. Craniopharyngioma. Endocrine Reviews. 2014; 35: 513–543.

[21] Evans JJ, Kenning TJ. Craniopharyngiomas: comprehensive diagnosis, treatment and outcome. 1st edn. Academic Press: London. 2014.

[22] Miller DC. Pathology of craniopharyngiomas: clinical import of pathological findings. Pediatric Neurosurgery. 1994; 21: 11–17.

[23] Prieto R, Pascual JM. Craniopharyngiomas with a mixed histological pattern: the missing link to the intriguing pathogenesis of adamantinomatous and squamous-papillary varieties? Neuropathology. 2013; 33: 682–686.

[24] Alli S, Isik S, Rutka JT. Microsurgical removal of craniopharyngioma: endoscopic and transcranial techniques for complication avoidance. Journal of Neuro-oncology. 2016; 130: 299–307.

[25] Mortini P, Gagliardi F, Bailo M. Losa M. Surgical Approach to Craniopharyngiomas: Transcranial Routes. In Lania A, Spada A, Lasio G (eds.) Diagnosis and Management of Craniopharyngiomas. Springer, Cham. 2016.

[26] Qiao N. Endocrine outcomes of endoscopic versus transcranial resection of craniopharyngiomas: A system review and meta-analysis. Clinical Neurology and Neurosurgery. 2018; 169: 107–115.

[27] Nie C, Ye Y, Wu J, Zhao H, Jiang X, Wang H. Clinical Outcomes of Transcranial and Endoscopic Endonasal Surgery for Craniopharyngiomas: A Single-Institution Experience. Frontiers in Oncology. 2022; 12: 755342.

[28] Mortini P, Losa M, Pozzobon G, Barzaghi R, Riva M, Acerno S, *et al*. Neurosurgical treatment of craniopharyngioma in adults

and children: early and long-term results in a large case series. Journal of Neurosurgery. 2011; 114: 1350–1359.
[29] Flitsch J, Müller HL, Burkhardt T. Surgical strategies in childhood craniopharyngioma. Frontiers in Endocrinology. 2011; 2: 96.
[30] Yamada S, Fukuhara N, Oyama K, Takeshita A, Takeuchi Y, Ito J, *et al*. Surgical outcome in 90 patients with craniopharyngioma: an evaluation of transsphenoidal surgery. World Neurosurgery. 2010; 74: 320–330.
[31] Kitano M, Taneda M. Extended transsphenoidal surgery for suprasellar craniopharyngiomas: infrachiasmatic radical resection combined with or without a suprachiasmatic trans-lamina terminalis approach. Surgical Neurology. 2009; 71: 290–8, discussion 298.
[32] Gallotti AL, Barzaghi LR, Albano L, Medone M, Gagliardi F, Losa M, *et al*. Comparison between extended transsphenoidal and transcranial surgery for craniopharyngioma: focus on hypothalamic function and obesity. Pituitary. 2022; 25: 74–84.
[33] Yamada S, Fukuhara N, Yamaguchi-Okada M, Nishioka H, Takeshita A, Takeuchi Y, *et al*. Therapeutic outcomes of transsphenoidal surgery in pediatric patients with craniopharyngiomas: a single-center study. Journal of Neurosurgery. Pediatrics. 2018; 21: 549–562.
[34] Zhang C, Ding X, Lu Y, Hu L, Hu G. Cerebrospinal fluid rhinorrhoea following transsphenoidal surgery for pituitary adenoma: experience in a Chinese centre. Rinoliquorrea dopo chirurgia dell'adenoma ipofisario con approccio transfenoidale: esperienza in un centro cinese. Acta Otorhinolaryngologica Italica. 2017; 37: 303–307.
[35] Laufer I, Anand VK, Schwartz TH. Endoscopic, endonasal extended transsphenoidal, transplanum transtuberculum approach for resection of suprasellar lesions. Journal of Neurosurgery. 2007; 106: 400–406.
[36] Sankhla SK, Jayashankar N, Khan GM. Extended endoscopic endonasal transsphenoidal approach for retrochiasmatic craniopharyngioma: Surgical technique and results. Journal of Pediatric Neurosciences. 2015; 10: 308–316.
[37] Liu JK, Christiano LD, Patel SK, Eloy JA. Surgical nuances for removal of retrochiasmatic craniopharyngioma via the endoscopic endonasal extended transsphenoidal transplanum transtuberculum approach. Neurosurgical Focus. 2011; 30: E14.
[38] Henderson F, Schwartz TH. Update on management of craniopharyngiomas. Journal of Neuro-oncology. 2022; 156: 97–108.
[39] Fan J, Liu Y, Pan J, Peng Y, Peng J, Bao Y, *et al*. Endoscopic endonasal versus transcranial surgery for primary resection of craniopharyngiomas based on a new QST classification system: a comparative series of 315 patients. Journal of Neurosurgery. 2021; 135: 1298–1309.
[40] Cao L, Wu W, Kang J, Cai K, Li C, Liu C, *et al*. Feasibility of endoscopic endonasal resection of intrinsic third ventricular craniopharyngioma in adults. Neurosurgical Review. 2022; 45: 1–13.
[41] Kassam AB, Gardner PA, Snyderman CH, Carrau RL, Mintz AH, Prevedello DM. Expanded endonasal approach, a fully endoscopic transnasal approach for the resection of midline suprasellar craniopharyngiomas: a new classification based on the infundibulum. Journal of Neurosurgery. 2008; 108: 715–728.
[42] Zhao R, Deng J, Liang X, Zeng J, Chen X, Wang J. Treatment of cystic craniopharyngioma with phosphorus-32 intracavitary irradiation. Child's Nervous System. 2010; 26: 669–674.
[43] Bartels U, Laperriere N, Bouffet E, Drake J. Intracystic therapies for cystic craniopharyngioma in childhood. Frontiers in Endocrinology. 2012; 3: 39.
[44] Desai SS, Paulino AC, Mai WY, Teh BS. Radiation-induced moyamoya syndrome. International Journal of Radiation Oncology, Biology, Physics. 2006; 65: 1222–1227.
[45] Steinbok P, Hukin J. Intracystic treatments for craniopharyngioma. Neurosurgical Focus. 2010; 28: E13.
[46] Zhang S, Fang Y, Cai BW, Xu JG, You C. Intracystic bleomycin for cystic craniopharyngiomas in children. The Cochrane Database of Systematic Reviews. 2016; 7: CD008890.
[47] Takahashi H, Nakazawa S, Shimura T. Evaluation of postoperative intratumoral injection of bleomycin for craniopharyngioma in children. Journal of Neurosurgery. 1985; 62: 120–127.
[48] Hukin J, Steinbok P, Lafay-Cousin L, Hendson G, Strother D, Mercier C, *et al*. Intracystic bleomycin therapy for craniopharyngioma in children: the Canadian experience. Cancer. 2007; 109: 2124–2131.
[49] Ferrantini M, Capone I, Belardelli F. Interferon-alpha and cancer: mechanisms of action and new perspectives of clinical use. Biochimie. 2007; 89: 884–893.
[50] Broggi G, Giorgi C, Franzini A, Leocata F, Riva D. Therapeutic Role of Intracavitary Bleomycin Administration in Cystic Craniopharyngioma. In Broggi G (ed.) Craniopharyngioma. Springer: Milano. 1995.
[51] Cavalheiro S, Dastoli PA, Silva NS, Toledo S, Lederman H, da Silva MC. Use of interferon alpha in intratumoral chemotherapy for cystic craniopharyngioma. Child's Nervous System. 2005; 21: 719–724.
[52] Kilday J, Caldarelli M, Massimi L, Chen RH, Lee YY, Liang M, *et al*. Intracystic interferon-alpha in pediatric craniopharyngioma patients: an international multicenter assessment on behalf of SIOPE and ISPN. Neuro-oncology. 2017; 19: 1398–1407.
[53] Yeung JT, Pollack IF, Panigrahy A, Jakacki RI. Pegylated interferon-α-2b for children with recurrent craniopharyngioma. Journal of Neurosurgery. Pediatrics. 2012; 10: 498–503.
[54] Kortmann R. Different approaches in radiation therapy of craniopharyngioma. Frontiers in Endocrinology. 2011; 2: 100.
[55] O'steen L, Indelicato DJ. Advances in the management of craniopharyngioma. F1000Research. 2018; 7: F1000 Faculty Rev-1632.
[56] Aggarwal A, Fersht N, Brada M. Radiotherapy for craniopharyngioma. Pituitary. 2013; 16: 26–33.
[57] Jimenez RB, Ahmed S, Johnson A, Thomas H, Depauw N, Horick N, *et al*. Proton Radiation Therapy for Pediatric Craniopharyngioma. International Journal of Radiation Oncology, Biology, Physics. 2021; 110: 1480–1487.
[58] Beltran C, Roca M, Merchant TE. On the benefits and risks of proton therapy in pediatric craniopharyngioma. International Journal of Radiation Oncology, Biology, Physics. 2012; 82: e281–e287.
[59] Boehling NS, Grosshans DR, Bluett JB, Palmer MT, Song X, Amos RA, *et al*. Dosimetric comparison of three-dimensional conformal proton radiotherapy, intensity-modulated proton therapy, and intensity-modulated radiotherapy for treatment of pediatric craniopharyngiomas. International Journal of Radiation Oncology, Biology, Physics. 2012; 82: 643–652.
[60] Friedman DL, Whitton J, Leisenring W, Mertens AC, Hammond S, Stovall M, *et al*. Subsequent neoplasms in 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. Journal of the National Cancer Institute. 2010; 102: 1083–1095.
[61] Merchant T, Indelicato D, Hua C, Wu S, Conklin H. Comparison of academic scores after proton and photon therapy in children and young adults with craniopharyngioma. Pediatric Blood & Cancer. 2017; 64: e26772.
[62] Leber KA, Berglöff J, Pendl G. Dose-response tolerance of the visual pathways and cranial nerves of the cavernous sinus to stereotactic radiosurgery. Journal of Neurosurgery. 1998; 88: 43–50.
[63] Kobayashi T, Kida Y, Mori Y, Hasegawa T. Long-term results of

gamma knife surgery for the treatment of craniopharyngioma in 98 consecutive cases. Journal of Neurosurgery. 2005; 103: 482–488.
[64] Chung WY, Pan DH, Shiau CY, Guo WY, Wang LW. Gamma knife radiosurgery for craniopharyngiomas. Journal of Neurosurgery. 2000; 93: 47–56.
[65] Amendola BE, Wolf A, Coy SR, Amendola MA. Role of radiosurgery in craniopharyngiomas: a preliminary report. Medical and Pediatric Oncology. 2003; 41: 123–127.
[66] Ohhashi G, Miyazaki S, Ikeda H, Hori T. Postoperative Long-term Outcomes of Patient with Craniopharyngioma Based on CyberKnife Treatment. Cureus. 2020; 12: e7207.
[67] Iwata H, Tatewaki K, Inoue M, Yokota N, Baba Y, Nomura R, *et al*. Single and hypofractionated stereotactic radiotherapy with CyberKnife for craniopharyngioma. Journal of Neuro-oncology. 2012; 106: 571–577.
[68] Lee M, Kalani MYS, Cheshier S, Gibbs IC, Adler JR, Chang SD. Radiation therapy and CyberKnife radiosurgery in the management of craniopharyngiomas. Neurosurgical Focus. 2008; 24: E4.
[69] Guimarães MM, Cardeal DD, Teixeira MJ, Lucio JEDC, Sanders FH, Kuromoto RK, *et al*. Brachytherapy in paediatric craniopharyngiomas: a systematic review and meta-analysis of recent literature. Child's Nervous System. 2022; 38: 253–262.
[70] Hasegawa T, Kondziolka D, Hadjipanayis CG, Lunsford LD. Management of cystic craniopharyngiomas with phosphorus-32 intracavitary irradiation. Neurosurgery. 2004; 54: 813–822.
[71] Voges J, Sturm V, Lehrke R, Treuer H, Gauss C, Berthold F. Cystic craniopharyngioma: long-term results after intracavitary irradiation with stereotactically applied colloidal beta-emitting radioactive sources. Neurosurgery. 1997; 40: 263–269; discussion 269–70.
[72] Rojas EL, Al-Dweri FMO, Lallena AM, Bodineau C, Galán P. Dosimetry for radiocolloid therapy of cystic craniopharyngiomas. Medical Physics. 2003; 30: 2482–2492.
[73] Sadeghi M, Karimi E, Sardari D. Monte Carlo and analytical calculations of dose distributions in craniopharyngioma cysts treated with radiocolloids containing 32P or 186Re. Applied Radiation and Isotopes. 2009; 67: 1697–1701.
[74] Yu X, Christ SM, Liu R, Wang Y, Hu C, Feng B, *et al*. Evaluation of Long-Term Outcomes and Toxicity After Stereotactic Phosphorus-32-Based Intracavitary Brachytherapy in Patients with Cystic Craniopharyngioma. International Journal of Radiation Oncology, Biology, Physics. 2021; 111: 773–784.
[75] Castle-Kirszbaum M, Shi MDY, Goldschlager T. Quality of Life in Craniopharyngioma: A Systematic Review. World Neurosurgery. 2022; 164: 424–435.e2.
[76] Castle-Kirszbaum M, Uren B, Goldschlager T. Anatomic Variation for the Endoscopic Endonasal Transsphenoidal Approach. World Neurosurgery. 2021; 156: 111–119.
[77] Karavitaki N, Brufani C, Warner JT, Adams CBT, Richards P, Ansorge O, *et al*. Craniopharyngiomas in children and adults: systematic analysis of 121 cases with long-term follow-up. Clinical Endocrinology. 2005; 62: 397–409.
[78] Wijnen M, van den Heuvel-Eibrink MM, Janssen JAMJL, Catsman-Berrevoets CE, Michiels EMC, van Veelen-Vincent MC, *et al*. Very long-term sequelae of craniopharyngioma. European Journal of Endocrinology. 2017; 176: 755–767.
[79] Sklar CA. Craniopharyngioma: endocrine abnormalities at presentation. Pediatric Neurosurgery. 1994; 21: 18–20.
[80] de Vries L, Lazar L, Phillip M. Craniopharyngioma: presentation and endocrine sequelae in 36 children. Journal of Pediatric Endocrinology & Metabolism. 2003; 16: 703–710.
[81] Hidalgo ET, Orillac C, Kvint S, McQuinn MW, Dastagirzada Y, Phillips S, *et al*. Quality of life, hypothalamic obesity, and sexual function in adulthood two decades after primary gross-total resection for childhood craniopharyngioma. Child's Nervous System. 2020; 36: 281–289.
[82] Clopper RR, Meyer WJ, Udvarhelyi GB, Money J, Aarabi B, Mulvihill JJ, *et al*. Postsurgical IQ and behavioral data on twenty patients with a history of childhood craniopharyngioma. Psychoneuroendocrinology. 1977; 2: 365–372.
[83] Erfurth E. Diagnosis, Background, and Treatment of Hypothalamic Damage in Craniopharyngioma. Neuroendocrinology. 2020; 110: 767–779.
[84] Özyurt J, Müller HL, Thiel CM. A systematic review of cognitive performance in patients with childhood craniopharyngioma. Journal of Neuro-oncology. 2015; 125: 9–21.
[85] Nuijts MA, Veldhuis N, Stegeman I, van Santen HM, Porro GL, Imhof SM, *et al*. Visual functions in children with craniopharyngioma at diagnosis: A systematic review. PLoS ONE. 2020; 15: e0240016.
[86] Erfurth EM, Holmer H, Fjalldal SB. Mortality and morbidity in adult craniopharyngioma. Pituitary. 2013; 16: 46–55.
[87] Pereira AM, Schmid EM, Schutte PJ, Voormolen JHC, Biermasz NR, van Thiel SW, *et al*. High prevalence of long-term cardiovascular, neurological and psychosocial morbidity after treatment for craniopharyngioma. Clinical Endocrinology. 2005; 62: 197–204.
[88] Pemberton LS, Dougal M, Magee B, Gattamaneni HR. Experience of external beam radiotherapy given adjuvantly or at relapse following surgery for craniopharyngioma. Radiotherapy and Oncology. 2005; 77: 99–104.
[89] Müller HL, Bueb K, Bartels U, Roth C, Harz K, Graf N, *et al*. Obesity after childhood craniopharyngioma–German multicenter study on pre-operative risk factors and quality of life. Klinische Padiatrie. 2001; 213: 244–249.
[90] Poretti A, Grotzer MA, Ribi K, Schönle E, Boltshauser E. Outcome of craniopharyngioma in children: long-term complications and quality of life. Developmental Medicine and Child Neurology. 2004; 46: 220–229.
[91] Visser J, Hukin J, Sargent M, Steinbok P, Goddard K, Fryer C. Late mortality in pediatric patients with craniopharyngioma. Journal of Neuro-oncology. 2010; 100: 105–111.
[92] Wu J, Wu X, Yang YQ, Ding H, Yang L, Bao YY, *et al*. Association of histological subtype with risk of recurrence in craniopharyngioma patients: a systematic review and meta-analysis. Neurosurgical Review. 2022; 45: 139–150.
[93] Gupta DK, Ojha BK, Sarkar C, Mahapatra AK, Sharma BS, Mehta VS. Recurrence in pediatric craniopharyngiomas: analysis of clinical and histological features. Child's Nervous System. 2006; 22: 50–55.
[94] Dandurand C, Sepehry AA, Asadi Lari MH, Akagami R, Gooderham P. Adult Craniopharyngioma: Case Series, Systematic Review, and Meta-Analysis. Neurosurgery. 2018; 83: 631–641.
[95] Muller HL. Childhood craniopharyngioma. Recent advances in diagnosis, treatment and follow-up. Hormone Research. 2008; 69: 193–202.
[96] Duff J, Meyer FB, Ilstrup DM, Laws ER, Schleck CD, Scheithauer BW. Long-term outcomes for surgically resected craniopharyngiomas. Neurosurgery. 2000; 46: 291–302; discussion 302–305.
[97] Park HJ, Dho Y, Kim JH, Kim JW, Park C, Kim YH. Recurrence Rate and Prognostic Factors for the Adult Craniopharyngiomas in Long-Term Follow-Up. World Neurosurgery. 2020; 133: e211–e217.
[98] Du C, Feng C, Yuan J, Yuan X. Ectopic recurrence of pediatric craniopharyngiomas after gross total resection: a report of two cases and a review of the literature. Child's Nervous System. 2016; 32: 1523–1529.
[99] Müller HL, Merchant TE, Puget S, Martinez-Barbera J. New outlook on the diagnosis, treatment and follow-up of childhood-

onset craniopharyngioma. Nature Reviews Endocrinology. 2017; 13: 299–312.
[100] Gorelyshev S, Savateev AN, Mazerkina N, Medvedeva O, Konovalov AN. Craniopharyngiomas: Surgery and Radiotherapy. Advances and Technical Standards in Neurosurgery. 2022; 45: 97–137.
[101] Joiner JB, Pylayeva-Gupta Y, Dayton PA. Focused Ultrasound for Immunomodulation of the Tumor Microenvironment. Journal of Immunology. 2020; 205: 2327–2341.
[102] Bunevicius A, McDannold NJ, Golby AJ. Focused Ultrasound Strategies for Brain Tumor Therapy. Operative Neurosurgery. 2020; 19: 9–18.
[103] Sainte-Rose C, Puget S, Wray A, Zerah M, Grill J, Brauner R, *et al*. Craniopharyngioma: the pendulum of surgical management. Child's Nervous System. 2005; 21: 691–695.
[104] de Vile CJ, Grant DB, Hayward RD, Kendall BE, Neville BG, Stanhope R. Obesity in childhood craniopharyngioma: relation to post-operative hypothalamic damage shown by magnetic resonance imaging. The Journal of Clinical Endocrinology and Metabolism. 1996; 81: 2734–2737.
[105] Puget S, Garnett M, Wray A, Grill J, Habrand J, Bodaert N, *et al*. Pediatric craniopharyngiomas: classification and treatment according to the degree of hypothalamic involvement. Journal of Neurosurgery. 2007; 106: 3–12.
[106] Yang L, Xie S, Tang B, Wu X, Tong Z, Fang C, *et al*. Hypothalamic injury patterns after resection of craniopharyngiomas and correlation to tumor origin: A study based on endoscopic observation. Cancer Medicine. 2020; 9: 8950–8961.
[107] Prieto R, Rosdolsky M, Hofecker V, Barrios L, Pascual JM. Craniopharyngioma treatment: an updated summary of important clinicopathological concepts. Expert Review of Endocrinology & Metabolism. 2020; 15: 261–282.
[108] Yaşargil MG, Curcic M, Kis M, Siegenthaler G, Teddy PJ, Roth P. Total removal of craniopharyngiomas. Approaches and long-term results in 144 patients. Journal of Neurosurgery. 1990; 73: 3–11.
[109] Jamshidi AO, Beer-Furlan A, Prevedello DM, Sahyouni R, Elzoghby MA, Safain MG, *et al*. A modern series of subdiaphragmatic craniopharyngiomas. Journal of Neurosurgery. 2018; 131: 526–531.
[110] Pan J, Qi S, Liu Y, Lu Y, Peng J, Zhang X, *et al*. Growth patterns of craniopharyngiomas: clinical analysis of 226 patients. Journal of Neurosurgery. Pediatrics. 2016; 17: 418–433.
[111] Yang F, Liu W, Cheng D, Zhang H, Li Z, Cao Z, *et al*. Multifactor Prognostic Evaluation of Postoperative Craniopharyngiomas. The Journal of Craniofacial Surgery. 2021; 32: 228–232.
[112] Liu Y, Qi S, Wang C, Pan J, Fan J, Peng J, *et al*. Pathological Relationship Between Adamantinomatous Craniopharyngioma and Adjacent Structures Based on QST Classification. Journal of Neuropathology and Experimental Neurology. 2018; 77: 1017–1023.
[113] Pascual JM, Prieto R, Rosdolsky M. Craniopharyngiomas primarily affecting the hypothalamus. Handbook of Clinical Neurology. 2021; 181: 75–115.
[114] Prieto R, Pascual JM, Rosdolsky M, Castro-Dufourny I, Carrasco R, Strauss S, *et al*. Craniopharyngioma adherence: a comprehensive topographical categorization and outcome-related risk stratification model based on the methodical examination of 500 tumors. Neurosurgical Focus. 2016; 41: E13.
[115] Pascual JM, Prieto R, Carrasco R, Barrios L. Duct-like diverticulum at the base of third ventricle tumors: a morphological signature diagnostic of papillary craniopharyngioma. Neurosurgical Review. 2022; 45: 3361–3379.
[116] Cao L, Wu W, Kang J, Qiao H, Yang X, Bai J, *et al*. Expanded Transsphenoidal Trans-Lamina Terminalis Approach to Tumors Extending into the Third Ventricle: Technique Notes and a Single Institute Experience. Frontiers in Oncology. 2021; 11: 761281.