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REVIEW

Modern treatment of craniopharyngioma to improve outcomes: evidence of a change of paradigm

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Abstract

Background Craniopharyngiomas, rare primary brain tumors of the pituitary-hypothalamic axis, frequently result in sicubstantial morbidity, including compromised quality of life, vision impairment, hypothalamic and endocrine dysfunction, and neuroendocrine disturbances. Of particular importance is the development of hypothalamic obesity, which affects up to 25% of patients at diagnosis and increases to 50% after treatment. Genotyping has revealed that over 90% of papillary craniopharyngiomas (PCP) harbor BRAF V600E mutations. Recent studies have demonstrated a significant reduction in tumor size with the use of BRAF-MEK inhibitors in PCP.

Methods We conducted a systematic review of recent literature on pretreatment or neo-adjuvant medical therapies, analyzing their effectiveness, safety, and sequelae following surgical treatment with this new approach.

Results At the time of this review, 15 studies involving more than 50 patients have been published, with a response rate of up to 90%.

Conclusion Based on this evidence, we propose a new treatment paradigm aimed at improving outcomes by maximizing relief from compressive symptoms while minimizing hypothalamic dysfunction.

Key words BRAF-MEK inhibitors · Papillary craniopharyngioma · Adamantinomatous craniopharyngioma · BRAF V600E mutation · Wnt/beta-catenin · Targeted treatment

Introduction

Craniopharyngiomas (CP) are rare, locally aggressive epithelial tumors that typically arise in the sellar and suprasellar regions of the skull. They originate from embryonic remnants of the craniopharyngeal duct. Although classified as benign (WHO grade 1), they exhibit local invasiveness, infiltrating adjacent structures such as the hypothalamus, pituitary gland, optic chiasm, and optic nerves, leading to significant morbidity and mortality either before or after treatment. While short-term prognosis is better in younger patients compared to adults (5-year survival rates of 83–96% versus 54–96%), long-term comorbidity outcomes show no substantial differences (62% versus 66–85% at 20 years) [1]. However, recent advances in diagnosis and therapy have improved survival rates and reduced complications.

CPs account for 1–3% of intracranial tumors, with an incidence of 0.5–2 cases per million/year [2] and a prevalence of 1–3 per 100,000. They exhibit a bimodal age distribution, with peaks between 5–15 years and in the fifth decade of life. They are the most common neuroepithelial

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intracranial neoplasm in children (5.3–15%) and the most common neoplasm of the hypophyseal fossa in this age group (80–90%). More than 50% of cases of the adamantinomatous subtype are diagnosed in patients under 20 years old. Tumors confined exclusively to the intrasellar region constitute 5–6% of cases, while 94–95% extend to the suprasellar area (purely suprasellar in 20–41% and parasellar in 20–30% of cases) [1].

There are two histologic subtypes: adamantinomatous and papillary (considered distinct tumor types in the 2021 WHO classification). The adamantinomatous craniopharyngioma (ACP) is the most frequent subtype, accounting for about 90% of cases, primarily seen in pediatric patients (5–11% of intracranial tumors in this age group) but also affecting adults. These tumors have both solid and cystic components. Papillary craniopharyngioma (PCP) is almost exclusively seen in adults aged 40–55 years and accounts for 10% of all cases [3]. Calcifications are rare in the papillary type. PCPs are well-circumscribed compared to the adamantinomatous type, and invasion of surrounding brain tissue is less common.

Recent data have provided important insights into the molecular pathogenesis and origin of CP, offering distinguishing features for both subtypes and identifying new molecular drug targets. The WNT signaling pathway is strongly implicated in the pathogenesis of ACP, with 95% of tumors harboring activating somatic mutations in exon 3 of the CTNNB1 gene, which encodes β-catenin. Activated WNT signaling influences tumor cell migration [4], and it has been shown that EGFR- and SHH signaling pathways are also upregulated in ACP and associated with tumor cell migration [2, 5, 6].

In 2020, an integrated proteogenomic characterization divided pediatric craniopharyngiomas into two subtypes:

1. Subtype C4 (Cranio/LGG-BRAFV600E-like): This group shows proteomic similarities with low-grade gliomas (LGG) harboring the BRAF V600E mutation, with high activation of the MEK/ERK and AKT/mTOR pathways.
2. Subtype C8 (Cranio/LGG-BRAF WT-like): This group is less proliferative and exhibits decreased activity in growth and proliferation pathways.

This characterization also found a strong association between CTNNB1 mutation and WNT pathway activation, with increased expression of beta-catenin. CTNNB1 elevates the expression of APC, GSK3A, and GSK3B. Although the CTNNB1 mutation was expected to activate TCF4, the study revealed that TCF4 has lower expression in these tumors, while TCF25 is overexpressed. It is suggested that TCF25 may mediate the effects of CTNNB1 in CP, representing a difference from other WNT-driven tumors [7].

Additionally, there is increased expression of immunosuppressive factors (e.g., IL-10, galectin-1) and pro-inflammatory cytokines (e.g., IL-1, IL-6) in the tumor microenvironment, providing a biological rationale for the use of monoclonal antibodies such as Tocilizumab in the treatment of ACP [6].

The molecular background of PCP initiation was largely unknown until exome sequencing studies revealed somatic BRAFp.V600E mutations (BRAFp.Val600Glu) in up to 95% of these tumors [4, 6, 8]. To date, no other recurrent mutations or genomic aberrations have been identified. The expression of oncogenic BRAF V600E is observed in the vast majority of tumor cells, conferring a proliferative advantage to SOX2-positive tumor cells [6].

The treatment of CP is challenging and requires a multidisciplinary approach. Historically, it has relied on surgical excision of most of the tumor tissue, aiming to preserve critical surrounding structures such as the hypothalamus, followed by radiotherapy [1, 4, 9, 10]. The diagnosis of CP is suspected based on clinical and radiological findings and confirmed through histological studies. Recent advances in molecular genetics have provided new perspectives for targeted therapy in PCP harboring BRAFp.V600E mutations, particularly in adult-onset PCP [2, 3].

Methods

The aim of this paper is to review general treatment outcomes, with a focus on new medical therapies for PCP. A systematic methodology was applied to this topic. A search of the most relevant papers in the PUBMED, Google Scholar, and MEDLINE databases was conducted using the following keywords: “craniopharyngioma AND therapy outcomes,” “craniopharyngioma AND target therapy,” “craniopharyngioma AND medical treatment,” “craniopharyngioma AND papillary,” “papillary AND craniopharyngioma AND medical treatment,” “papillary AND craniopharyngioma AND BRAF inhibitors,” and “papillary AND craniopharyngioma AND BRAF/MEK inhibitors.”

A secondary search was performed using the bibliographies of the articles identified in the primary search. Articles were reviewed by title and abstract for relevance, and if the relevance was unclear, the full text was reviewed. The search was limited to human studies and English-language publications.

Results

The initial search yielded 9 articles, one of which was excluded. The secondary search identified 143 articles, of

which 87 were excluded due to irrelevance, leaving 56 articles for this review.

Clinical evaluation

The most common symptoms arise from the expansive nature of CP and/or the development of intracranial hypertension. Craniopharyngiomas often cause endocrine deficiencies (75–90%), leading to growth delay in children (60–80%), central hypothyroidism (40–50%), hypogonadism (50–70%), adrenal insufficiency (20–40%), and diabetes insipidus (10–20%). Neurological symptoms (50–80%) include headaches (60–80%) and, in some cases, obstructive hydrocephalus with intracranial hypertension (10–30%). Visual disturbances (40–80%) such as bitemporal hemianopsia (50–70%) and decreased visual acuity (40–60%) are common. Metabolic issues like obesity (30–50%) arise due to hypothalamic dysfunction. Cognitive and behavioral disorders (20–40%) may include memory and learning difficulties, as well as personality changes [1, 2, 11–13].

Visual disturbances occur in 50% of cases due to intracranial hypertension or mass effect, which can lead to permanent vision loss. Motor function alterations of cranial nerves (II, IV, and VI) occur due to invasion of the cavernous sinuses [1, 2, 11]. Endocrine involvement is more evident in childhood, as hypothalamic-pituitary dysfunction affects normal development and growth. Since these tumors grow slowly, symptoms are insidious and non-specific, often leading to a delay in diagnosis of 1 to 2 years.

In childhood, the most frequent symptoms/signs include vision loss, symptoms of intracranial hypertension (irritability, nausea, vomiting, papilledema, and even macrocephaly if cranial sutures are not closed), and growth failure. In preadolescence, visual disturbances (loss of visual acuity and visual field defects) and pubertal development disorders are prominent [2, 12]. In adulthood, the most common symptoms are hypogonadism with erectile dysfunction and oligomenorrhea (45–65%) and visual disturbances [1]. Hyperphagia and obesity, polyuria, and polydipsia due to ADH deficiency, associated with significant hypothalamic involvement, can occur at any age [2, 11].

When CP involves the hypothalamic area, other non-endocrine manifestations may be present, including sleep disruption, behavioral disorders, and difficulties with memory and learning. Depending on the extent of hypothalamic damage, these symptoms may partially or completely remit after therapy or become chronic. Modern therapies aim to avoid such outcomes by reducing the extent of resection, minimizing damage to adjacent structures, and reducing the need for retreatment [11, 12, 14, 15].

Radiologic assessment

CPs generally measure more than 2 cm (14–20% > 4 cm, 58–76% between 2 and 4 cm, and 4–28% <2 cm). The classic radiological appearance is a solid mass (18–39%) or a cystic-solid mass (46–64%) with varying degrees of calcification. Hydrocephalus (20–38%) is more common in children (about 50% at diagnosis) [2]. A parasellar calcified cystic lesion, even evident on plain skull radiography, is highly suggestive of adamantinomatous CP. Careful imaging evaluation at diagnosis is critical to define the topographic location of the tumor, its relationship with the visual pathways, and potential adhesions to surrounding structures. This stratification can guide neurosurgical therapy and predict surgical outcomes, particularly regarding hypothalamic dysfunction.

Both computed tomography (CT) and magnetic resonance imaging (MRI) are essential. CT is useful for assessing calcification, while MRI, including T1- and T2-weighted images (WI) with turbo spin echo sequences before and after intravenous gadolinium (Gd) injection, should be performed and evaluated by an experienced neuroradiologist. If possible, MRI should be performed using a 3 Tesla (3 T) unit. The imaging protocol should include:

- T1WI TSE before and after Gd injection: 3D sagittal (0.7–1 mm) with multiplanar reconstruction in axial and coronal planes, or alternatively 2D (2 mm) in sagittal and coronal planes.
- T2WI TSE before Gd injection: 2D coronal (2 mm) centered on the pituitary gland and tumor.
- 3D high-resolution T2WI balanced steady-state gradient echo sagittal (0.7–1 mm) sequence (CISS, FIESTA) centered on the tumor and the floor of the third ventricle, or alternatively 2D sagittal (2 mm) acquisition.
- Multi-echo gradient recalled echo (GRE) T2* or susceptibility-weighted imaging (SWI) axial (2 mm) centered on the pituitary region to detect calcium or blood.
- 2D axial FLAIR sequences (3 mm) and T2WI covering the whole brain.

These sequences are crucial for differentiating CP from other etiologies such as germinoma, glioneuronal tumor, hemangioblastoma, pituicytoma, and Langerhans histiocytosis [2, 6, 14].

ACPs are typically voluminous, multiloculated, or solid-cystic, with predominantly cystic components and walls that frequently contain calcifications. In contrast, PCPs have a significant solid portion or are uniloculated, mostly non-calcified, and develop more proximally to the infundibulum or third ventricle compared to ACPs [16, 17]. The

evaluation of the third ventricle is crucial for prognostic implications and surgical planning. An MRI-based classification by Gaillard et al. [11] describes three subtypes based on the tumor's relationship with the hypothalamus:

- Type 1: Infra-hypothalamic tumor location, inferior to the hypothalamus without involvement.
- Type 2: The tumor perforates the floor of the third ventricle, involving the hypothalamus.
- Type 3: Supra-hypothalamic tumor with clear identification of the third ventricle floor, strictly located below the tumor.

MRI and CT are complementary imaging modalities crucial for initial diagnosis, predicting adhesions to surrounding structures, and guiding surgical resection. They are also used for post-treatment follow-up to assess treatment-related changes and clinical outcomes [18].

In the near future, radiomic algorithms may allow for more specific differentiation between CP subtypes. This methodology is already proving useful for fine assessment of various tumors, and recent studies have highlighted its potential for CP characterization [12, 19–21]. It is currently debated whether precise histological subtype identification is possible through radiologic tumor characteristics. In 2022, Pascual et al. [16] identified a novel morphological sign pathognomonic of PCPs, known as a "basal duct-like recess" or "basal diverticulum," which may obviate the need for biopsy in some cases, particularly in older individuals or when surgical treatment is not planned. With the advent of radiomics, it is likely that MRI-based identification algorithms will soon be developed, potentially eliminating the need for biopsies in ambiguous cases [19–22].

Histologic confirmation

Although some radiologic signs are pathognomonic for CP, a confirmatory biopsy is still performed in many centers for histological diagnosis and molecular characterization to guide targeted medical treatment. Given the relatively low risk of surgical biopsy compared to resection and the impressive results of BRAF-targeted therapy, a "biopsy-first approach" is now supported by several groups [8, 11, 23]. Histopathological examination confirms the CP diagnosis and provides information on the tumor type based on specific staining patterns [5]. Immunohistochemical staining for BRAF and nuclear beta-catenin in PCP and ACP, respectively, can complement molecular studies for BRAF and CTNNB1 mutations, especially when tissue samples are limited. Additionally, circulating cell-free DNA is being validated for CP mutational assessment, like its use in other tumors [24, 25].

Surgical treatment

Surgical treatment has historically been the mainstay of CP management, aiming to obtain a histological diagnosis and remove as much tumor tissue as possible while preserving surrounding neural structures [26–28]. Team experience is the most critical factor in achieving extensive resection or substantial debulking with minimal complications. Recent studies have shown a decrease in severe obesity and pituitary deficiencies with more conservative, non-radical surgical approaches [4, 13].

In 2011, a multinational prospective trial by Müller et al. [29] concluded that surgical lesions of the anterior and posterior hypothalamic areas were associated with a higher increase in body mass index compared to patients without or with only anterior lesions. Treatment in high-volume centers was associated with less radical surgeries, lower rates of complete resection, and fewer hypothalamic sequelae. The study emphasized that CP treatment should be confined to experienced multidisciplinary teams.

In a recent study [28], 34 endoscopic endonasal transsphenoidal surgeries (EEA) achieved total resection in 64.5% of cases and near-complete resection in 22.5%. First-time surgery patients had a 73.1% total resection rate, compared to only 20% in recurrent cases. However, recurrence rates and damage to surrounding structures remained high (20–30% at 2 years) [28], including hypothalamic dysfunction, optic nerve and cerebral vessel lesions, and pituitary deficiencies. These rates decreased significantly when BRAF-targeted therapy was included in the multimodal treatment.

In high-volume centers, total resection rates can reach up to 70%. Despite this, relapses may occur, and early treatment with surgery, radiotherapy, or a combination of both is essential for disease control [30, 31].

In a systematic review and meta-analysis conducted in 2022 [32], the endoscopic endonasal approach (EEA) was associated with a higher rate of Gross Total Resection (GTR) compared to transcranial approaches (TCA) (77.2% vs. 61.5%). Patients treated with EEA also exhibited better visual improvement (60.7% vs. 32.7%) and a lower risk of visual deterioration compared to TCA. Both approaches carried similar risks of panhypopituitarism and diabetes insipidus, though EEA showed a trend toward lower endocrine complications. However, TCA was associated with a significantly lower risk of cerebrospinal fluid (CSF) leakage (1.2% vs. 9.9%), while the risk of meningitis was comparable between the two approaches.

These findings were confirmed in 2024 by Li et al. [33], who concluded that EEA offers several advantages, including higher GTR rates in pediatric patients, improved visual outcomes, and lower recurrence and hypopituitarism rates. However, EEA also presents a higher risk of CSF

leakage. Despite this, EEA remains a favorable approach for CP resection, particularly in adults, due to its association with lower rates of infection, stroke, hydrocephalus, and mortality.

A recently published French series [2, 11] reported long-term disease control in 100, 92, and 83% of type 1, 2, and 3 CP subtypes, respectively, based on lesion topography. This is particularly relevant for type 3 CP, which historically has demonstrated poorer surgical outcomes. PCPs are frequently found among noncalcified type 3 tumors, reaching 100% of cases in the French series [11]. Given that approximately 90% of these patients harbor BRAF mutations, targeted medical treatment represents a promising avenue for improving outcomes. Consequently, the traditional first-line treatment paradigm is being questioned: should surgery remain the initial approach, or should medical treatment take precedence, potentially reducing tumor volume before surgery or radiotherapy, thereby facilitating a less radical surgical intervention and reducing the required radiation field?

On the other hand, little is known about the biological determinants of CP recurrence. However, recent studies have identified chromosomal arm copy number variations in recurrent ACPs, which may aid in identifying high-risk patients [34]. The MAPK/ERK pathway is activated in nearly all recurrent ACP cases. According to the French Endocrine Society guidelines [2], in adults, the standard transsphenoidal approach is recommended for suprasellar and intrasellar craniopharyngiomas without supradiaphragmatic extension. For tumors with suprasellar transdiaphragmatic extension, the extended transsphenoidal approach is preferred. In addition to endoscopic endonasal techniques, various transcranial surgical approaches remain in use, tailored to tumor size and location. The goal is to optimize tumor accessibility while minimizing traction on surrounding structures and avoiding damage to the third ventricle and optic pathways. Transcranial approaches may be advantageous for tumors without pituitary stalk involvement in clearly suprasellar locations. This technique has regained interest for its potential to spare hypothalamic and pituitary function and is now included in modern treatment protocols [11]. The transcranial approach, thus, is primarily recommended for CPs strictly confined to the third ventricle, with no extension to the pituitary stalk and located above the hypothalamic floor without perforating it. The EEA is not recommended for intraventricular tumors due to the high risk of hypothalamic syndrome [4, 28, 30–33]. In children, the endoscopic transventricular approach is a safe and effective alternative for the initial treatment of cystic suprasellar craniopharyngiomas, offering advantages such as reduced invasiveness, shorter operative time, less blood loss, and lower recurrence rates compared to traditional microscopic surgery [35, 36].

Other alternatives for the treatment of predominantly cystic CPs, such as intracavitary installation of cytotoxic drugs, are no longer in use.

Radiation therapy

Modern radiotherapy techniques allow precise dose delivery while minimizing exposure to adjacent healthy tissues. Several radiotherapy modalities are currently available for CP treatment:

- Normofractionated radiotherapy: the most commonly used approach, delivering total doses of 50.04–59.4 Gy over 28–33 fractions (1.8 Gy per fraction), with a median dose of 54 Gy in 30 fractions.
- Stereotactic radiosurgery (SRS): a single-fraction treatment with marginal doses of 13–16 Gy, requiring careful patient selection.
- Hypofractionated stereotactic radiotherapy (HFSRT): administered in 2–10 fractions with marginal doses of 13–25 Gy.
- Intensity-modulated radiation therapy (IMRT): a modern technique that enhances precision and minimizes exposure to healthy tissues.
- Proton therapy: an advanced modality that improves dose accuracy and reduces side effects. A study reported a 5-year progression-free survival (PFS) rate of 93.6%, though 95% of patients experienced hormone deficiencies post-treatment [37–47].

Recent meta-analyses suggest that conventional radiotherapy yields superior 5-year PFS compared to SRS (0.843; 95% CI: 0.767–0.898) [41]. Postoperative radiotherapy, whether following total or subtotal resection, significantly reduces recurrence rates, achieving tumor control in more than 95% of patients at three-year follow-up [37]. Proton therapy has shown promising results, with improved cognitive function preservation in treated patients [42].

Medical therapy: preoperative and postoperative approaches

The therapeutic approach to CP, incorporating novel medical treatments, is illustrated in Figs. 1, 2.

Papillary craniopharyngioma

The discovery of the BRAF V600E mutation in >95% of PCP cases has revolutionized treatment, enabling targeted therapy with BRAF and MEK inhibitors. These agents significantly reduce tumor size, facilitating less aggressive surgery and minimizing surgical sequelae, potentially decreasing the need for radiotherapy [6].

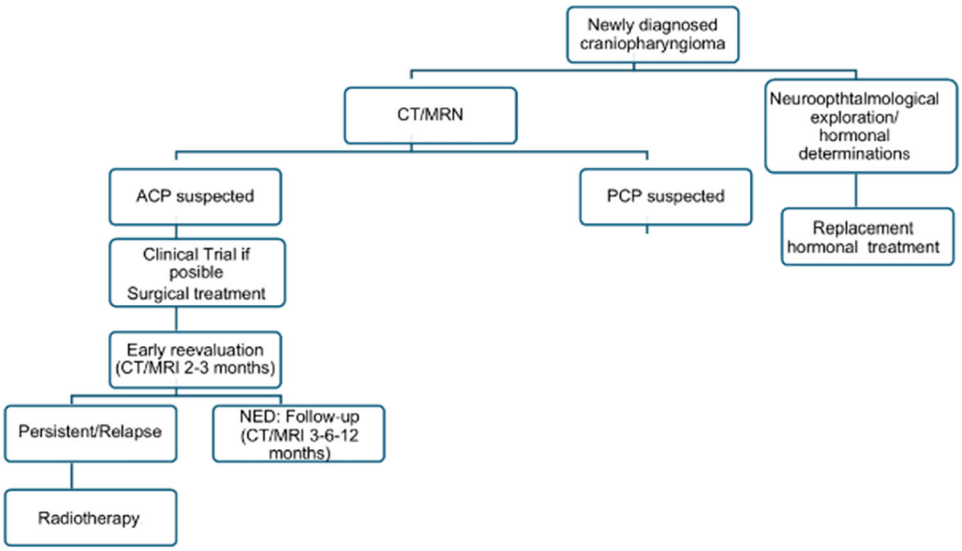

Fig. 1 Proposed ACP multimodal treatment approach through multidisciplinary committee assessment. NED non evident disease, PR partial response, R response, ACP adamantinomatous Craniopharyngioma, PCP papillary Craniopharyngioma

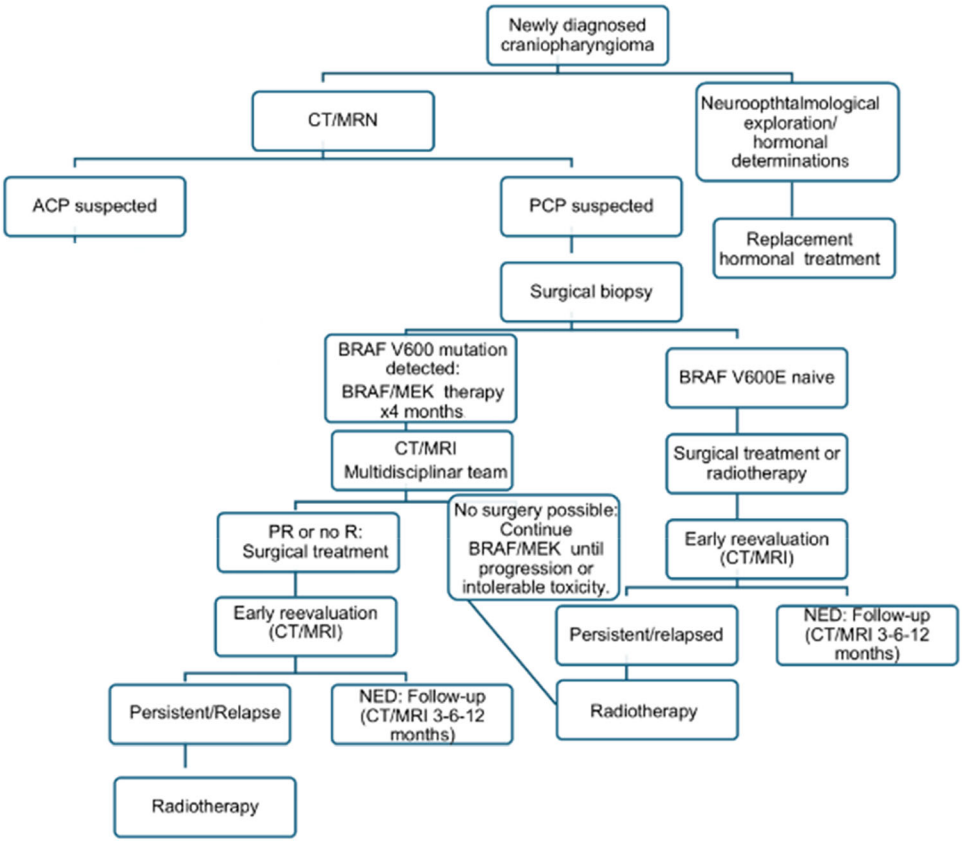

Fig. 2 Proposed PCP multimodal treatment approach through multidisciplinary committee assessment. NED non evident disease, PR partial response, R response, ACP adamantinomatous Craniopharyngioma PCP papillary Craniopharyngioma

Recent studies have demonstrated remarkable tumor shrinkage following BRAF/MEK inhibitor therapy. Juratli et al. [48] and Calvanese et al. [8] reported a 95% reduction in tumor volume with Dabrafenib (150 mg twice daily) and Trametinib (2 mg once daily), with good tolerance. Brastianos et al. [49] conducted a landmark study on 16 BRAF-mutated PCP patients, demonstrating a 91% median tumor reduction, with 87% PFS at 12 months and 58% at 24 months. Another study by De Alcubierre et al. [3] confirmed these findings, showing that 94% of patients achieved a partial response or better.

While these therapies offer unprecedented efficacy, their optimal duration remains unclear [6, 50, 51]. Additionally, cost and accessibility present challenges to widespread implementation.

Adamantinomatous craniopharyngioma

In ACP, CTNNB1 mutations drive Wnt/β-catenin pathway activation in ~95% of cases. Targeted therapies such as MEK inhibitors (binimetinib) and anti-IL-6 monoclonal antibodies (Tocilizumab) are under investigation [52–56]. Clinical trials are also evaluating Tizaterkib (ERK1/2 inhibitor), Nivolumab (anti-PD1), and Tovorafenib (pan-RAF kinase inhibitor) for CP treatment (NCT05465174).

Conclusions

Historically, CP has been managed with surgery and radiotherapy, often at the cost of significant morbidity. Advances in molecular biology have identified targetable mutations, such as BRAF V600E in PCP, enabling precision medicine approaches. The introduction of BRAF/MEK inhibitors has led to substantial tumor shrinkage, improved surgical outcomes, and a shift in treatment paradigms.

The management of CP should be guided by multidisciplinary teams, incorporating expertise from neurosurgeons, endocrinologists, neurooncologists and neuroradiologists. With the advent of targeted therapies, CP treatment is entering a new era, where medical management plays a central role.

Data availability

No datasets were generated or analysed during the current study.

Author contributions All authors contributed to the writing of the manuscript. The manuscript has been reviewed by all authors.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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