

# Clinical, Pathological and Surgical Risk Factors Associated with Craniopharyngioma Recurrence: A Literature Review

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## Abstract

**Objective:** This review article attempts to examine and provide an overview of the risk factors associated with craniopharyngioma recurrence. **Methods:** A literature review of articles relating to the recurrences of craniopharyngioma and the clinical, molecular prognostic indicators of recurrence and treatment outcomes was performed retrospectively. **Results:** A total of 107 studies which described specific risk factors related to craniopharyngioma recurrence were identified which included but not limited to 54 retrospective case series, 7 systematic reviews, 21 laboratory reports, 13 case reports and 12 literature reviews. **Conclusion:** Based on the evidence identified in this review, the risk factors for recurrence in craniopharyngioma management are interrelated in a complex way, and surgery with or without adjuvant radiotherapy is reported to be of long-term benefit, but a disparity in findings suggests no definitive consensus on the risk factors of craniopharyngioma recurrence. More high-quality research is needed.

## Keywords

Craniopharyngioma, Recurrence, Risk Factors, Subtotal Resection

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## 1. Introduction

Craniopharyngiomas (CPs) are benign tumor epithelial neoplasms of the sellar and parasellar region occurring in all age groups, postulated to arise from pathological alteration of epithelial cell remnants of Rathke's pouch and the craniopharyngeal duct [1]. CPs account for less than 5% of all intracranial tumors [2]

and possess a characteristic unpredictable growth pattern and a tendency to invade critical neurovascular structures. Tumor recurrence is a common observation following primary treatment of CP [3] and contributes significantly to the higher mortality and morbidity rates than those with primary CPs [4]. While the management of primary CPs is challenging, the treatment of recurrent CPs is even more exacting and variable [5] [6]. Currently, treatment of recurrent CP involves gross-total resection oriented surgical removal, in combination with or without adjuvant radiotherapy [7] [8], gamma knife surgery [9] [10] [11], stereotactic intracavitary brachytherapy [12], ommaya reservoir placement [13], intratumoral bleomycin [14] and systematic chemotherapy [15]. However, the role of clinical and histopathological features that might be predictors of recurrence/regrowth has not been clearly elucidated in published literature [16].

In the present review, we examined the current literature on the purported risk factors for recurrence, encompassing the epidemiologic, clinical, histopathological and molecular factors, with the aim to provide an overview of the published data regarding their association with CP recurrence. We also reviewed large retrospective recurrent CP series and case reports that specifically evaluated the presumed factors for CP recurrence and explore future trends in the treatment.

## **2. Methods**

A thorough search of published literature relating to CP recurrence was performed through PubMed and Elsevier-Science Direct databases, mainly utilizing the key word craniopharyngioma, and additional key words such as recurrence, risk factors, subtotal resection and treatment. A literature review of articles relating to the recurrences of craniopharyngioma and the clinical, molecular prognostic indicators of recurrence and treatment outcomes was performed retrospectively. A total of 107 studies which described specific risk factors related to craniopharyngioma recurrence were identified which included but not limited to; 54 retrospective case series, 7 systematic reviews, 21 laboratory reports, 13 case reports and 12 literature reviews.

## **3. Discussion**

### **3.1. Overview of Potential Risk Factors for CP Recurrence**

#### **3.1.1. Definition of Recurrence and Regrowth Craniopharyngioma**

Recently, despite the advancement in micro-neurosurgical techniques and neuroimaging modalities to improve preoperative planning and postoperative care, CP recurrence has remained a well acknowledged conundrum in many treatment centers. There is vast variability in the definition of CP recurrence and regrowth throughout the literature due to the differing methods of assessing and defining recurrence but also variance in the growth potential of the tumor in different individuals. In this paper, we define CP recurrence as evidence of remnant tumor observed on postoperative image studies of the follow-up period

despite undergoing previous gross total resection (GTR) or subtotal resection (STR) according to the operating neurosurgeon; or despite an initial negative control postoperative follow-up MRI study [5]. In addition, the term regrowth refers to the growth of a known tumor remnant following intentional STR or partial resection in follow-up imaging studies [6].

### 3.1.2. Recurrence and Epidemiologic Factors

Age at the time of treatment is also an important factor, with higher morbidity being assumed more in younger patients than adults, although a number of studies have reported conflicting results with no consensus its association with recurrence rate (RR). According to the literature, exclusive pediatric series have reported recurrence rates ranging from 9% to 24.5% [17] [18] [19] [20] [21]. Whereas some authors have noted young age [17] [19] as a recurrence risk factor, others adult age [22], most cohorts have not found a significant difference in the recurrence rate between children and adults [4] [6] [16] [23] [24] [25] [26]. Similarly, role of sex as a predictive factor is still under debate; inasmuch as some studies found a significant correlation between the rate of CP recurrence and the male sex [6] [27], others reported no association with sex whatsoever [16] [19] [25] [26] [28].

### 3.1.3. CP Recurrence and Clinical Manifestation

The biological behavior of CPs varies from patient to patient in that while some remain stable even up to 30 years before symptomatic recurrence [29], others may grow rapidly within an erratic period of time [2]. It has been reported that most recurrences appear during the first 5 years following treatment [6] [30]. Similar to primary CPs, the clinical symptoms of RCPs are inconstant, on account of the variable topographical location [31]. CPs of suprasellar region commonly present with headache, visual field defects, and endocrine dysfunctions [32]. A few studies have reported visual symptoms at presentation [24], symptoms of intracranial hypertension at presentation [27] and severe hydrocephalus [17] as significant factors associated with recurrence. However, other cohorts reported no significant differences between patients with primary CP and RCP in the neurological, endocrinological, visual, or functional symptoms [20] [23] [33] nor the presence of hydrocephalus [19] [25].

### 3.1.4. CP Recurrence and Tumor Morphologic Features

An issue of specific interest is the relevance of tumor morphology in CP recurrence to which current literature bears inconsistent findings. Tumor size is likely to be a predictive factor because increased recurrence rates have been shown in tumors with a diameter larger than 3 cm [5] [17] [20] [34] [35]; other studies did not support these findings [27] [36]. Aside from tumor size, other physical attributes such as tumor adherence [37], intrasellar location [28], third ventricle remnants [38] and cystic tumors [34] [39] have been proposed to be clinical predictors of recurrence. In other studies, none of tumor brain invasion [21] [34], tumor extension [19], tumor consistency [26] nor tumor location [19] [22] [25]

[35] and presence of xanthogranulomatous tissue [16], were found to be of significant importance in tumor recurrence. Clinically, the presence of calcifications could suggest a possible involvement with CP recurrence given the fact that tight adherences to neurostructures have often led to incomplete resection even in some of the most skilled hands [40]. On the contrary, Elliot *et al.* in a cohort of eighty-six pediatric patients showed that the absence or presence of minimal residual calcification does not have an impact on the risk of CP recurrence after GTR [41].

### 3.1.5. CP Recurrence and Radiologic Findings

Ohmori *et al.* in a pediatric series of twenty-seven pediatric patients surgically treated for CPs observed a significant low recurrence rate for patients in whom early postoperative MRI reveals complete CP removal [42], in agreement with Mortini's findings [21]. On the other hand, Eldevik *et al.* [43] studied the radiologic and histologic characteristics of CPs and could not identify any imaging characteristics of tumors that corresponded to a high or low rate of recurrence, as supported by other studies. [23] [44]

### 3.1.6. CP Recurrence and Histopathologic or Molecular Features

Over the past 30 years, studies into the histopathologic nature of CPs have thrown more light into understanding its pathogenesis. Still, the genetic and molecular basis of the recurrence CP is yet to be well elucidated. However, advances in immunohistochemical studies and direct genetic sequencing have attempted to exemplify the molecular pathogenesis of CP initiation, growth, and recurrence [3]. There are two subtypes of CPs, adamantinomatous (ACP) and papillary (PCP) that may differ clinically and histologically but also share overlapping characteristics. Histologically, ACPs contain nodules of wet keratin, regressive changes like fibrosis, calcifications, old hemorrhages, cholesterol deposits; a mixture of cystic and solid portions, whorl-like structures, ghost cells, intense surrounding gliosis, and profuse Rosenthal fiber formation [1] [45] and nucleocytoplasmic accumulation of  $\beta$ -catenin [45] [46]. On the other hand, the PCP subtype is distinctly characterized by a solid, papillary growth pattern missing the wet keratin, cystic appearance and regressive elements of the ACP subtype [44].

At the molecular level, extensive studies of whole-exome sequencing data of craniopharyngiomas have revealed that the ACP and PCP subtypes have distinct molecular underpinnings, each driven characteristically by mutual exclusivity of mutations in a single well-established oncogene: CTNNB1 (P-catenin gene) in the ACP form and BRAF in the papillary form as a result of activation of the MAPK pathway [47] [48] [49]. Tena-Suck *et al.* observed that the presence of whorl-like arrays was associated with recurrence/regrowth of CP [16] which could likely be caused by mutations of the P-catenin gene. Interestingly, several studies have reported no significant differences in recurrence rate and between adamantinomatous type and papillary type [6] [21] [24] [26] [34] [50]. Whilst

no definitive tumor markers that predict recurrence have not been identified, several recent studies (**Table 1**) which have attempted to shed more light on some important prognostic factors that may correlate with CP recurrence have shown that RCPs displayed a significantly higher expression of these postulated biomarkers than primary tumors.

**Table 1** summarizes some of the potential biomarkers of CP recurrence.

Other studies have supported the role of Ep-CAM overexpression in tumor cell proliferation and recurrence in other brain tumors [58] [59]. Conversely, others studied molecular proteins which have been associated with recurrence but have not been found significant include laminin 8 and BCL-2 [51]. Apart from its likely involvement in maintaining the proliferative activity of tumoral cells, increased p53 expression has been purported as a marker of malignancy transformation [60]. Of particular note, Prieto *et al.* [5] and Tena-Suck [16] reported a positive association of p53 expression with CP recurrence, though other studies obviate these findings [60] [61].

The use of proliferation-associated antigen Ki-67 and mitotic index for the histological evaluation of different tumors has been widely reported [5] [18] [62]. On the contrary, other studies found no correlation between Ki-67 and risk of recurrence of CPs [22] [28] [63]. Duo *et al.* [64] proposed that the very low level of MIB-1-LI in residual tumor remnants negates their role in initiation of recurrence. In disagreement, Hussain *et al.* [3] purported that rapid recurrence may be a function of the immune response in the tumor microenvironment. Lefranc and colleagues [61] attributed the adhesiveness of CPs to the proximity tissues such as optical chiasm and pituitary stalk to interactions between vitronectin, CP-alpha (2beta1) integrin and collagens, proteins expressed by peritumoral tissue. Furthermore, they demonstrated that galectin-4 expression was associated with a significant delay in recurrence. In another study, Xu and colleagues found that minichromosome maintenance protein 6 (MCM6) label

**Table 1.** Craniopharyngioma recurrence and predictive biomarkers of recurrence.

Author, Year	Number of cases in study	Predictive Biomarker	Postulated Role in RCP pathogenesis
Tena-Suck <i>et al.</i> [51] 2009	40 ACPs	Ep-CAM, PTTG-1	Ep-CAM expression may be involved with invasiveness and proliferation; PTTG-1 expression may suggest hypophyseal metaplasia
Ebrahimi <i>et al.</i> [52] 2013	43	Osteonectin	Marker of tumor invasion and aggressive behavior
Gong <i>et al.</i> [53] 2014	45 ACPs	CXCL12/CXCR4	Play a role in regulating the directional migration and proliferation of tumor cells
Stache <i>et al.</i> [54] 2014	66 ACPs, 21 PCPs	claudin-1 (CLDN1)	Altered distribution of CLDN1 affects cell mobility and tumor invasiveness
Samis <i>et al.</i> [55] 2016	23	miR-132	Downregulation of miR-132 appears to be a marker of aggressiveness and also plays a role in epithelial-mesenchymal transition
Li <i>et al.</i> [56] 2016	50	FABP5/CRABP II	FABP5/CRABP II determines cellular response to physiological level of retinoic acid which may be involved in tumor cell apoptosis
Wang <i>et al.</i> [57] 2017	65 ACPs	Annexin A2 (AnxA2)	affects cell mobility and tumor progression

index (LI) was significantly higher in primary CPs than in RCPs [65]. Whether angiogenesis-related factors play a part in CP recurrence is still a matter of contention. In line with this observation, Sun *et al.* compared the expression of angiogenesis-related factors in 4 recurrent and 6 nonrecurrent tumors, they found that expression of PDGFR-alpha and FGF-2 were significantly higher for recurrent tumors ( $P = 0.02$  and  $P = 0.01$ ), thus suggesting that selective PDGFR-alpha blockers may offer a novel therapeutic option for CP treatment [66], although they no significant correlation with VEGF, in parallel with Xu *et al.* findings [65], but in disagreement, Agozzino [22] found a significantly higher VEGF expression in recurrences than in primary CP.

### **3.1.7. CP Recurrence and Malignancy and Ectopic Occurrence.**

Despite their reportedly benign nature, a few cases of malignant transformation of primary CP diagnosis on recurrence [67] [68] [69] have been reported but the exact pathogenesis and the biological behavior of malignant change in recurrent CP are not well elucidated in although a possible causative association with radiation therapy has been postulated [68] [70]. Ectopic recurrence of CP after primary surgical management is no longer a rare phenomenon as several reports have been documented [71] [72] [73] [74] with a widely accepted pathophysiological hypothesis which evolves around tumor seeding occurs either along the surgical route, or at a distal location in the subarachnoid space [71] [73].

## **3.2. CP Recurrence and Treatment of Recurrent Craniopharyngioma**

### **3.2.1. CP Recurrence and Surgical Management**

The optimal management of recurrent craniopharyngioma (RCP) is still disputable [75]. However, several authors have stressed that radical surgery should be the first therapeutic option for RCP with acceptable morbidity and mortality risks similar to that of primary tumors [6] [18] [20] [76] [77] [78]. Conversely, others have reiterated that secondary surgery for RCP is associated with a low cure rate and a high risk of complications [19] [37] [75]. In addition, recurrence rates following radical tumor resection vary widely and have been reported as 9% to 65% [19] [21] [23] while others noted that the incidence of recurrence did not differ significantly with radicality at surgery [4]. In general, several authors have echoed that surgical treatment for RCP is considered more challenging than primary surgery due to scarring, absence of gliosis reaction in RCP, tight adherences and morphological changes due to irradiation [2] [37] [75]. Most published literature has consistently reported residual tumor and the extent of resection as the strongest predictive factor for CP recurrence [6] [16] [17] [20] [25] [34] [37] [63]. In contrast, other studies have downplayed the role of residual CP as a predictive of recurrence [4] [40] [64].

Accordingly, due to the variable location of CPs or RCPs in proximity with neurostructures, some surgeons have advocated for intentional subtotal or partial removal for reasons not limited to; hypothalamic adherence of CP which is

associated with postoperative morbidity and mortality [36]; an inadequate view of the tumor due to large tumor extensions and inappropriate surgical approach; presence of major calcifications [37] which poses a risk of damage to the hypothalamus and the optic chiasm [37] [77]; firm adherence of the tumor capsule to relatively large perforating vessels or to large basal arteries as it is safer to leave minor residual portions of tumor in anticipation of vascular damage [32] [79]. Prieto demonstrated that in an effort to preserve the hypothalamus, the CP remnants may lead to erratic tumor recurrence [38], whereas studies by Li *et al.* [80] mentioned otherwise. It has been noted significant number of patients with residual tumors remain stable for a long time [36]. Similarly, Hoffman *et al.* recommended that radical surgery is not an appropriate treatment strategy in patients with hypothalamic involvement [45]. In a recent study, Clark *et al.* reviewed a total of 109 studies describing the extent of resection resulting in a cohort of 531CP patients and 377 recurrences. They found no difference in the progression-free survival (PFS) of 1 year (89% vs 84%) or 5-year (77% vs 73%) between the groups who underwent GTR and STR combined with radiation. Their results suggest that STR + XRT of pediatric CP is associated with similar rates of tumor control as GTR [7]. These findings were similar to those of Schoenfeld *et al.* [26] and Yang [81] and colleagues. What remains unclear is whether the preservation of pituitary stalk at resection represents a recurrence prognostic factor because some studies have demonstrated a correlation with recurrence [82] [83] whereas other studies reported no significant association with CP recurrence [33] [83]. In some population of CP patients, although Growth hormone replacement therapy (GHRT) may pose a concern for stimulating tumor regrowth, several studies have demonstrated that long-term GHRT is not associated with risk of CP recurrence [84] [85] [86].

Throughout literature, CPs and RCPs have been widely reported to present in the variable locations [31]. On these grounds, several surgical approaches in recurrent CP series including transsphenoidal, subfrontal, trans-lamina terminalis, subtemporal and transcallosal approach [2] [6] [75] [78] [87] [88] have been advocated with the effort to reduce morbidity and mortality risks, although the optimum surgical approach is still debatable. In a recent publication, Morisako *et al.* attempted to devise an anatomical subclassification of CPs for achieving aggressive surgery [89]. In a similar vein, Prieto *et al.* [5] stressed that evasion of hypothalamic injury should be the primary goal in any surgical planning, including the choice of approach and preplanned extent of removal. A few authors have strongly recommended the use of endonasal route [2] [90] for recurrent tumors especially patients in whom the initial surgery was transcranial, asserting the advantage it offers of facing the tumor upon dural opening without brain retraction while optimizing visualization of the relevant anatomy via a direct surgical trajectory.

### **3.2.2. CP Recurrence and Radiotherapy**

The role of adjuvant radiotherapy (RT) in the management of RCP is well do-

cumented in literature with numerous studies showing lower recurrence rates after GTR or STR [2] [8] [18] [26] [43]. In contrast, other studies have reported that the incidence of recurrence did not differ significantly with respect to post-operative radiotherapy [4] [16] [91]. In a review of pediatric CP surgical series, Tomita *et al.* demonstrated that RT was effective for recurrent tumors and should be considered being the primary treatment for recurrences or difficult tumors, which are not amenable to total resections [19]. The optimum timing of RT for RCP is still controversial. Fisher *et al.* observed that short times to recurrence may result from the tendency to delay radiotherapy [40]. Additionally, Elliot *et al.* the authors observed that withholding irradiation or other adjuvant therapy in the setting of minimal residual calcification without enhancing tumor [41].

### 3.2.3. CP Recurrence and Gamma Knife Surgery (GKS)

The efficacy of GKS as a valuable adjuvant treatment modality for RCP has been well documented [11] [91] [92] despite its limitation to small size tumors (<3 cm). A study by Park *et al.* [9] showed that STR followed by GKS results in a lower recurrence rate than neuroendoscopy-GKS and GKS alone group much as the latter provided better preservation of endocrine function. Others studies have proposed CP histological subtype [93] intratumoral homogeneous irradiation using multiple isocenters [94], distance from the tumor to the optic nerves, and tumor radiosensitivity [10] as prognostic factors that favor successful treatment outcome in RCP. In a large cohort of one hundred CP cases, Kobayashi *et al.* [95] demonstrated that tumor diameter and radiation dose were the only the significant prognostic factors related to recurrence of CP.

### 3.2.4. CP Recurrence and Other Conventional Treatment Modalities

1) **Intracavitary Brachytherapy:** Recent studies investigating the efficacy of intracavitary brachytherapy have shown that inasmuch as it may offer a treatment option for cystic CPs, its use is limited by the fact that it does not limit growth of solid tumor parts or deter formation of new CP cysts [12] [96].

2) **Intracystic Bleomycin Therapy:** Hader *et al.* [97] reported significant tumor control with use of intratumoral bleomycin for cystic CPs, while avoiding potentially harmful surgical or radiotherapy related risks in the pediatric population. Reported complications related with this treatment include bleomycin leakage and toxicity, vasculopathy [98] and fatal toxic effects [99]. However, importantly, Zhang [14] and colleagues argued the rational use of intracystic bleomycin due to lack of RCTs, quasi-randomised trials or CCTs of the treatment of cystic CPs in children.

3) **Pegylated interferon- $\alpha$ -2b:** Yet another systematic conventional therapy [100] reportedly used in treatment of cystic recurrent CPs and some studies have shown its efficacy in children [101], however, its toxicity and optimum dosage obviate its importance and suggestively large series are necessary to establish its long term benefit.

### 3.3. Future Perspectives

The modern era has witnessed a surge in advancement of the diagnostic techniques, imaging modalities, immunohistochemical and genetic studies aimed at understanding molecular pathogenesis of CPs and RCPs. In effect, trials of specific therapeutics for CPs have been explored in various *in vivo* studies and possibly RCTs. Simon *et al.* reported part of the successful use of , a BRAF inhibitor vemurafenib with excellent tumor response for treatment of PCP [102]. Li [103] and colleagues suggested all-trans retinoic acid (ATRA) as a potential therapeutic agent for CP chemotherapy given its efficacy at pharmacological level induced craniopharyngioma cell apoptosis via increasing FABP5/CRABPII ratio and inhibiting NF-kappaB signaling pathway (107). Similarly, Sun *et al.* [66] suggested the possible use of selective PDGFR-a blockers for CPs given the higher expression of PDGFR-a and FGF-2 in RCPs versus primary CPs as reported in a recent study. In a recent study, Gump [104] and associates reported several notable significantly overexpressed genes of kinase inhibitors and EGFR pathways in ACPs comparable to normal brain tissue, pediatric brain tumors, normal pituitary, and pituitary tumors, suggesting their potential role as new pharmacological agents for pediatric CP treatment. In another recent study, Uto *et al.* [105] described the potential use of Non-coplanar volumetric-modulated arc therapy (VMAT) in effectively reducing radiation doses to the bilateral hippocampus, comparison to dynamic conformal arc therapy (DCAT).

In summary, randomized control trials (RCTs) and more comprehensive studies targeting genomic modifiers influencing cell survival, angiogenesis, invasion, and recurrence are necessary. These studies in reality may take many years before being successfully rendered expedient for clinical applications but will guide the development of genetically engineered animal models that more accurately epitomize human CPs, providing a remarkable ability to develop and ratify optimal therapeutic regimens for individuals with recurrent CPs. However, even though RCTs are the highest level of evidence, data from non-RCT cohorts offers valuable information given the clinical rarity and impact of CPs to constitute large cohorts.

### 4. Conclusion

Based on the evidence identified in this review, the risk factors for recurrence in craniopharyngioma are interrelated in a complex way, and surgery with or without adjuvant radiotherapy is reported to be of long-term benefit, but a disparity in findings suggests no definitive consensus on the risk factors of craniopharyngioma recurrence. More high-quality research is needed.

### Conflicts of Interest

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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### **List of Abbreviations**

CP	Craniopharyngioma
ACP	Adamantinomatous Craniopharyngioma
PCP	Papillary Craniopharyngioma
RCP	Craniopharyngioma
CT	Computed Tomography
MRI	magnetic Resonance Imaging
GTR	Gross Total Resection
STR	Subtotal Resection
RT	Radiation Therapy
GKS	Gamma Knife Surgery
SRS	Stereotactic Radiosurgery
RR	Recurrence Rate
RCTs	Randomized Control Trials
GHRT	Growth Hormone Replacement Therapy
H.E	Hematoxylin and Eosin Staining