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Review Articles

Chinese guidelines for the diagnosis and treatment of Craniopharyngioma in children (2025)

Zhixiong Lin [a,*], Jie Ma [b,**], Yonggao Mou [c,***], Songtao Qi [d,****], Xuejun Yang [e,*****], Jianguo Xu [f,******], Yi Lin [a], Yi Liu [d], Chuan Zhao [a], Wenhao An [a], Feng Wan [g], Songbai Gui [h], Gao Zeng [i], Ping Liang [j], Yiguang Chen [c], Yang Zhao [k], Mingwang Zhu [l], Chunde Li [m], Jian Gong [m], Yongxin Wang [n], Yaming Wang [h], Jie Zhao [o], Yan Ju [p], Ye Song [q], Xiaosheng He [r], Xingfu Wang [s], Xiaofang Yan [t], Xianxin Qiu [u], Hao Li [v], Yang Wang [u], Rong Zhang [w], Jie Gong [x], Xueling Qi [y], Ming Ge [z], Julei Wang [aa], Qingguo Li [ab], Jun Fan [d], Xiaobing Jiang [ac], Shibin Sun [ad], Wenzhong Mei [ae], Zheming Fang [af], Song Han [a], Bo Zhang [a]

[a] *Department of Neurosurgery, Sanbo Brain Hospital, Capital Medical University, Beijing, 100093, China*
[b] *Department of Neurosurgery, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, 200100, China*
[c] *Department of Neurosurgery/Neuro-oncology, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-sen University Cancer Center, Guangzhou, 510060, China*
[d] *Department of Neurosurgery, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong, 510515, China*
[e] *Department of Neurosurgery, Beijing Tsinghua Changgung Hospital, Tsinghua University, Tsinghua University School of Clinical Medicine, Beijing, 102218, China*
[f] *Department of Neurosurgery, West China Hospital of Sichuan University, Chengdu, 610044, China*
[g] *Department of Neurosurgery, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, 510080, China*
[h] *Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, 100070, China*
[i] *Department of Neurosurgery, Xuanwu Hospital, Capital Medical University, Beijing, 100037, China*
[j] *Department of Neurosurgery, Children's Hospital of Chongqing Medical University, Chongqing, 400014, China*
[k] *Department of Pediatric Neurosurgery, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, 200092, China*
[l] *Department of Radiology, SanBo Brain Hospital, Capital Medical University, Beijing, 100093, China*
[m] *Department of Neurosurgery, Beijing TianTan Hospital, Capital Medical University, Beijing, 100050, China*
[n] *Department of Neurosurgery, Neurosurgery Centre, The First Affiliated Hospital of Xinjiang Medical University, Xinjiang, 830054, China*
[o] *Department of Neurosurgery, Xiangya Hospital, Central South University, Changsha, 410008, China*
[p] *Department of Neurosurgery, West China Hospital, Sichuan University, Chengdu, 610041, China*
[q] *Department of Neurosurgery, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangdong Provincial Clinical Research Center for Child Health, Guangzhou, 510515, China*
[r] *Department of Neurosurgery, Shenzhen Hospital of Southern Medical University, Shenzhen, 518101, China*
[s] *Department of Pathology, The First Affiliated Hospital of Fujian Medical University, Fuzhou, 350005, China*
[t] *Department of Endocrinology, The First Affiliated Hospital of Fujian Medical University, Fuzhou, 350005, China*
[u] *Department of Radiation Oncology, Huashan Hospital, Fudan University, Shanghai, 200040, China*
[v] *Department of Neurosurgery, Affiliated Pediatric Hospital, Fudan University, Shanghai, 201100, China*
[w] *Department of Neurosurgery, Huashan Hospital, Fudan University, Shanghai, 201107, China*
[x] *Department of Neurosurgery, Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan, 250012, China*
[y] *Department of Pathology, Sanbo Brain Hospital, Capital Medical University, Beijing, 100093, China*
[z] *Department of Neurosurgery, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, 100045, China*

Sponsored by: Pediatric Neurosurgery Group, Neurosurgery Branch of the Chinese Medical Association; Neuro-oncology Expert Committee of the Chinese Society of Clinical Oncology; and Neuro-oncology Professional Committee of the China Anti-Cancer Association.

* Corresponding authors. Department of Neurosurgery, Sanbo Brain Hospital, Capital Medical University, Beijing, 100093, China
** Corresponding authors. Department of Neurosurgery, Xihua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, 200100, China
*** Corresponding authors. Department of Neurosurgery/Neuro-oncology, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-sen University Cancer Center, Guangzhou, 510060, China
**** Corresponding author. Department of Neurosurgery, Nanfang Hospital, Southern Medical University, Guangzhou, 510515, Guangdong, China
***** Corresponding author. Department of Neurosurgery, Beijing Tsinghua Changgung Hospital, Tsinghua University, Tsinghua University School of Clinical Medicine, Beijing, 102218, China
****** Corresponding author. Department of Neurosurgery, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, 510080, China
E-mail addresses: linzx@ccmu.edu.cn (Z. Lin), majie@xinhuamed.com.cn (J. Ma), mouyg@sysucc.org.cn (Y. Mou), qisongtaosjwk@163.com (S. Qi), ydenny@126.com (X. Yang), xujg@scu.edu.cn (J. Xu).

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[aa] Department of Neurosurgery, Second Affiliated Hospital of Air Force Military Medical University, Xi'an, 710038, China
[ab] Department of Neurosurgery, Tianjin Huanhu Hospital, Tianjin, 300350, China
[ac] State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-sen University Cancer Center, Guangzhou, 510060, China
[ad] Department of Gamma-Knife Center, Beijing Neurosurgical Institute, Beijing Tiantan Hospital, Capital Medical University, Beijing, 100070, China
[ae] Department of Neurosurgery, The First Affiliated Hospital of Fujian Medical University, Fuzhou, 350005, China
[af] Department of Radiology, The First Affiliated Hospital of Fujian Medical University, Fuzhou, 350005, China

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ABSTRACT

This guideline was developed under the auspices of the Pediatric Neurosurgery Group of the Neurosurgery Branch of the Chinese Medical Association, the Neuro-oncology Expert Committee of the Chinese Society of Clinical Oncology, and the Neuro-oncology Professional Committee of the China Anti-Cancer Association. Craniopharyngioma is the most common tumor in the sellar turcica region among children, with the majority being adamantinomatous craniopharyngioma (ACP) and a smaller proportion being papillary craniopharyngioma (PCP). Management of craniopharyngioma involves not only tumor control but also the treatment of tumor-related hypothalamic dysfunction and pituitary endocrine disorders. To standardize the diagnosis and management of pediatric craniopharyngioma, this guideline incorporates evidence from 398 literature references. It provides recommendations on diagnostic evaluation, surgical strategies, radiotherapy principles, prognostic assessment, follow-up and long-term management, and targeted therapy. This guideline is intended to serve as a reference for healthcare professionals engaged in pediatric neuro-oncology. Recommendations were developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology, taking into account the quality of evidence, clinical applicability, and expert consensus. Key recommendations are supported by explanatory rationale. The guideline were reviewed and approved by 35 multidisciplinary experts and 6 external reviewers, followed by formal voting on each recommendation. For areas lacking high-quality evidences, future well-designed clinical trials are recommended to validate and update these recommendations.

This guideline is sponsored by the Pediatric Neurosurgery Group, Neurosurgery Branch of the Chinese Medical Association, the Neuro-oncology Expert Committee of the Chinese Society of Clinical Oncology, and the Neuro-oncology Professional Committee of the China Anti-Cancer Association.

Craniopharyngioma is a rare intracranial tumor in children, accounting for 1.2% to 4.6% of all pediatric intracranial tumors [1–3]. Childhood-onset craniopharyngiomas represent a distinct and clinically significant subgroup [4,5] Incidence, treatment and survival of patients with craniopharyngioma in the surveillance, epidemiology and end results program. Histologically, they are traditionally classified into adamantinomatous craniopharyngioma (ACP) and papillary craniopharyngioma (PCP) subtypes [6]. The 2021 WHO Classification of Tumors of the Central System (5th version) further defines ACP and PCP as distinct entities, highlighting their differences in molecular profiles and clinical behavior [7]. Epidemiological studies indicate that ACP is more common in children, whereas PCP occurs almost exclusively in adults, accounting for only about 25% of adult craniopharyngiomas [8]. To standardize the management of pediatric craniopharyngioma, this guideline provides evidence-based recommendations for healthcare professionals involved in patient care. It covers the following key areas: diagnostic evaluation, surgical approaches, radiotherapy principles, prognostic assessment, follow-up, long-term management, and targeted therapy. The recommendations were developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (see Table 1), incorporating available evidence, clinical applicability, and expert consensus. Key recommendations include explanatory notes. The guidelines were reviewed and validated by 35 multidisciplinary experts and 6 external reviewers. Areas with limited evidence are suggested for refinement through future clinical trials. Compared with existing international reviews and guidelines—most of which address adult or mixed-age populations—this guideline is restricted to childhood-onset disease, integrates the China-derived, origin-based QST classification, proposes for the first time an integrated clinical–pathological–therapeutic prognostic risk-scoring model, and synthesizes the large-volume experience of multiple Chinese high-volume centers (e.g., Sanbo Brain Hospital, Xinhua Hospital, Nanfang Hospital). We regard the origin-based surgical algorithm and the prognostic scoring model as the principal novel contributions.

1. Methodology of guideline development

This guideline was developed through a systematic review of domestic and international literature and consensus statements on pediatric craniopharyngioma, supplemented by an expert discussion. A multidisciplinary writing group, including experts in neurosurgery, neuropathology, neuroimaging, radiotherapy, endocrinology, and pediatric oncology, drafted and revised the content in three stages.

Stage 1: The Pediatric Neurosurgery Group of the Neurosurgery Section of the Chinese Medical Association, the Neurological Tumor Expert Committee of the Chinese Society of Clinical Oncology, and the Neuro-Oncology Committee of the Chinese Anti-Cancer Association defined the scope, objective, and topics of the guideline. The writing group was established, and responsibilities were assigned.

A systematic literature search was conducted in PubMed, Embase, and other databases for articles published between January 1, 2014, and December 31, 2024. Key search terms included “craniopharyngioma”, “pediatric”, “endoscopic endonasal approach”, “radiation therapy”, and

Table 1
GRADE system: Levels of evidence and strength of recommendations.

Category	Description
Level of evidence	
High	Further research is very unlikely to change confidence in the effect estimate
Moderate	Further research may have an important impact and may change the estimate
Low	Further research is very likely to have an important impact and change the estimate
Very low	Any estimate of effect is very uncertain
Strength of recommendation	
Strong	Benefits clearly outweigh risks and burdens
Weak	Benefits and risks are closely balanced or uncertain

specific targeted therapies (e.g., BRAF inhibitors) (Fig. 1. Literature review process). The search strategy is detailed in Supplementary material 1.

Stage 2: The core working group of the guidelines drafted the initial version, which was revised to address the needs of clinical practitioners at different levels and to ensure applicability in primary healthcare settings.

Stage 3: An external review panel evaluated the content through a structured review and voting process (Table 2). The external review panel comprised specialists in neurosurgery, endocrinology, pediatrics, radiology, rehabilitation medicine, psychology, and representatives from the Chinese Craniopharyngioma Patients' Support Group. The member list is provided in the"**External Review Panel Roster.**" Consensus was defined as an agreement of >80% among the panel members. The strength of recommendation (Strong vs. Weak) was determined based on the sum of "Highly recommended", "Recommend", and "Agree" votes exceeding 80% for a strong recommendation.

In this guideline, recommendations are derived from evidence quality and expert consensus to establish 'best practice recommendations' (gold standard). Where applicable—such as for certain diagnostic evaluations and follow-up schedules—we also define 'minimum acceptable standards' based on local resources and clinical feasibility. For instance, the sections on imaging, endocrine function, and neuropsychological testing differentiate between ideal and minimum required assessments..

2. Overview

2.1. Definition and epidemiology

The peak incidence of craniopharyngioma in children occurs between 5 and 14 years of age, with no significant gender predilection [4,9]. We defined the age range for children in this guideline as 0 to 18 years. This range includes the peak age of incidence for childhood craniopharyngioma (5–14 years), while taking into account the epidemiological characteristics of craniopharyngioma, as well as Chinese laws, ethics, and cultural context. It should be noted that the age threshold defining "children" varies across countries and regions; the 0–18-year range adopted here reflects the Chinese context and may not be directly comparable to definitions used elsewhere. These tumors arise from remnants of the craniopharyngeal duct epithelium or Rathke's cleft, often exhibiting mixed solid and cystic components with frequent calcification. Despite its benign histology, craniopharyngioma often exhibits locally aggressive behavior akin to malignancy [10].

Pediatric craniopharyngiomas are categorized into two types: (1) ACP, the most common subtype in children, characterized by the coexistence of solid and cystic components, as well as high incidence of calcification (~90%). The histological features of ACP typically show epithelial tumor cells arranged in nests and trabeculae with stellate reticulum and "wet keratin" formation [11]. ACP is associated with mutations in the *CTNNB1* gene, which encodes β-catenin [12]. (2)PCP, rare in children [13–17], accounts for less than 2% of cases in children, is mostly solid with minimal cystic change or calcification. Histologically, it exhibits well-differentiated squamous epithelium in a papillary or perivascular arrangement. PCP is associated with *BRAF V600E* mutations [18].

Although PCP is classically regarded as an adult-predominant subtype, molecularly confirmed pediatric PCP is exceedingly rare, accounting for less than 2% of childhood craniopharyngiomas in molecular diagnostic series. Because pediatric PCP has been only sparsely addressed in international guidelines, recent pediatric and multicenter Chinese studies provide important complementary evidence. These studies indicate that pediatric PCP retains the defining BRAF V600E-driven molecular identity of adult PCP, while pediatric cases may differ in clinical presentation, age-related treatment

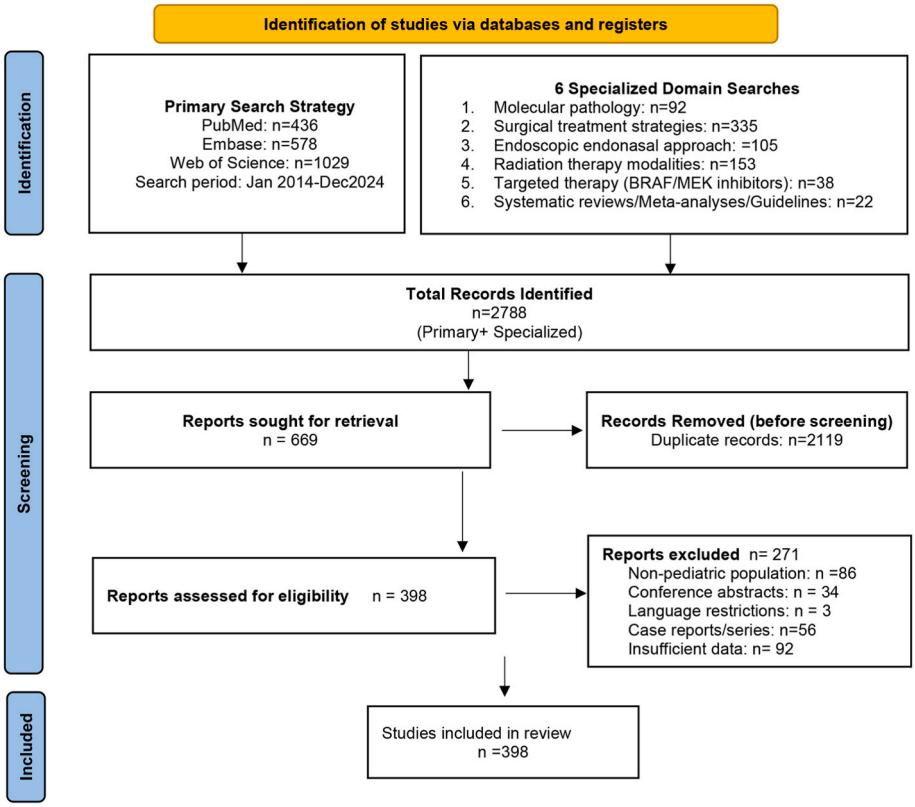


Fig. 1. Literature review process.

Table 2
Level of recommendation (%).

Recommendation	Contents	Highly recommended (%)	Recommend (%)	Agree (%)	Disagree (%)
1	Children presenting with headaches, visual impairment, or endocrine abnormalities (e.g. growth failure, diabetes insipidus) should undergo prompt neuroimaging (CT/MRI) to facilitate early diagnosis and intervention.	94%	6%	0%	0%
2	Prognostic evaluation should include age, presence of hydrocephalus, and postoperative diabetes insipidus.	71%	29%	0%	0%
3	Preoperative CT should be considered for evaluating calcification and bony anatomy, particularly for ACP or when evaluating transsphenoidal surgical approaches. Non-contrast CT is the first-line modality in emergencies (e.g., acute hydrocephalus or herniation) for rapid assessment. Contrast-enhanced CT is indicated for tumor characterization if MRI is contraindicated. However, if MRI has clearly defined the tumor characteristics and none of the above indications (calcification assessment, surgical planning for transsphenoidal approach, or emergency setting) are present, CT is not mandatory.	89%	3%	9%	0%
4	MRI is the preferred imaging modality for pediatric craniopharyngioma due to superior soft tissue resolution, which is critical for surgical planning.	83%	14%	3%	0%
5	Systematic pre- and postoperative assessment of hypothalamic-pituitary function is recommended and should be conducted by an experienced pediatric/pituitary endocrinologist in a dedicated pituitary center or MDT setting. Dynamic testing should be used as clinically indicated.	86%	11%	3%	0%
6	Neuropsychological and cognitive assessments should be performed before and after surgery, as well as during long-term follow-up, using culturally appropriate tools. These should be integrated into long-term follow-up.	26%	49%	26%	0%
7	A comprehensive ophthalmologic evaluation is recommended for all patients at diagnosis and during follow-up.	66%	26%	9%	0%
8	A standardized preoperative protocol including imaging, endocrine, visual, and cognitive assessments is recommended. A multidisciplinary team (MDT) discussion is encouraged for diagnostic accuracy and treatment planning. It is recommended that pediatric craniopharyngioma patients be referred to and managed within a Pituitary Tumor Center of Excellence (PTCOE)—a designated high-volume center providing a fixed multidisciplinary team, standardized care pathways, and 24-h endocrine and intensive-care support. This PTCOE model of centralized management extends beyond ad hoc MDT discussion and has been associated with higher rates of safe resection and better endocrine and functional outcomes.	60%	31%	6%	3%
9	Surgical resection with histopathological confirmation is recommended for symptomatic patients or those with clear radiological evidence of craniopharyngioma.	71%	29%	0%	0%
10	Reoperation should be considered for recurrent or progressive tumors after risk assessment.	54%	40%	6%	0%
11	Gross total resection is not recommended for tumors with extensive hypothalamic involvement (Puget grade 2). Subtotal resection with radiotherapy is preferred to reduce severe complications.	49%	29%	17%	6%
12	Surgery is not recommended for patients with severe medical comorbidities. Non-surgical options should be considered.	46%	31%	20%	3%
13	Preoperative adjuvant therapies (e.g., intracystic therapy) may be considered for high-risk or complex tumors to facilitate safer resection.	17%	31%	26%	26%
14	Treatment decisions should be made by an MDT.	46%	43%	11%	0%
15	Surgery is recommended as the first-line treatment for craniopharyngioma in children, aiming at total tumor resection while preserving vital functional structures to improve overall and progression-free survival. The extent of resection should be individualized according to the degree of hypothalamic involvement, and gross total resection should not be pursued when it would compromise hypothalamic function (see Recommendation 11).	80%	20%	0%	0%
16	The choice between EEA and TCA should be based on tumor anatomy, hypothalamic involvement, third-ventricle extension, surgeon experience, and MDT assessment, with the primary goal of maximizing surgical safety and functional preservation rather than maximizing the rate of total resection.	63%	31%	6%	0%
17	Preserve the pituitary stalk whenever possible. If the tumor is densely adherent, prioritize stalk function with subtotal resection and radiotherapy over stalk sacrifice, which should only be a last resort due to increased long-term complications.	49%	34%	17%	0%
18	For tumors with definite involvement of the hypothalamus and demonstration of thalamic injury, if the surgeon assesses that total resection will result in further functional impairment, a strategy of subtotal resection combined with radiotherapy is recommended to ensure local control while reducing serious postoperative complications.	38%	35%	21%	6%
19	Comprehensive preoperative assessment of the functional status of the hypothalamus is recommended as a key decision-making basis for developing an individualized resection strategy.	54%	29%	17%	0%
20	It is recommended that for cystic predominant lesions or those with acute manifestations of intracranial hypertension, prior treatment with drainage of cystic fluid and reduction of intracranial pressure by drugs should be considered to alleviate acute symptoms and optimize the conditions for subsequent treatment.	17%	37%	26%	20%
21	It is strongly recommended that surgery for craniopharyngioma in children be performed by highly qualified and experienced neurosurgeons with the support of a multidisciplinary team.	85%	9%	6%	0%
22	Dexamethasone may be used perioperatively for cerebral edema.	18%	33%	45%	3%
23	Vasopressin receptor antagonists are not routinely recommended for hyponatremia due to risk of triphasic response.	26%	47%	24%	3%
24	Hyponatremia should be evaluated and managed based on etiology.	50%	29%	18%	3%

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Table 2 (*continued*)

Recommendation	Contents	Highly recommended (%)	Recommend (%)	Agree (%)	Disagree (%)
25	Polyuria should be evaluated for central diabetes insipidus and other causes.	59%	29%	9%	3%
26	Preoperative correction of adrenal insufficiency and hypothyroidism is recommended.	58%	33%	9%	0%
27	Postoperative endocrine function should be assessed and managed long-term.	65%	29%	6%	0%
28	Histopathological and molecular testing should be performed to guide diagnosis and treatment.	74%	20%	6%	0%
29	Histopathological diagnosis should be complemented by characterization of the defining driver alterations—CTNNB1 (ACP) and BRAF V600E (PCP). In routine practice, mutation-specific immunohistochemistry (nuclear β-catenin for ACP; VE1/BRAF V600E for PCP) is the minimum acceptable standard and is usually sufficient for diagnosis. Because immunohistochemistry detects the downstream protein change as a surrogate, definitive confirmation of the underlying mutation requires a molecular technique (Sanger sequencing or next-generation sequencing); this should be reserved for cases with equivocal immunohistochemistry, atypical histology, or when mutation confirmation is required for targeted-therapy eligibility or clinical-trial enrollment.	57%	31%	9%	3%
30	For recurrent tumors, reoperation is an important option, but the risks and benefits should be carefully evaluated. If surgery is not suitable, radiotherapy or other adjuvant therapies may be considered. For residual tumors after subtotal resection, especially those at risk of progression, postoperative adjuvant radiotherapy (under appropriate age and resource conditions) is an effective means of tumor control.	44%	29%	24%	3%
31	Radiotherapy modality and timing should be individualized.	47%	32%	18%	3%
32	Proton therapy may be considered to reduce radiation exposure to normal tissues. Proton beam therapy should be considered/prioritized for pediatric patients when available, to reduce integral dose to the developing brain.	21%	32%	44%	3%
33	A CTV margin of 5 mm is recommended.	10%	65%	26%	0%
34	Conventional radiotherapy doses of 50.4–54.0 Gy in 28–30 fractions are standard. SRS doses of 12–14 Gy may be used for small lesions.	16%	56%	28%	0%
35	Targeted therapies may be considered within clinical trials or with full informed consent after MDT discussion. For recurrent or refractory ACP.	24%	38%	38%	0%
36	BRAF/MEK inhibitors should be considered for BRAF-mutated PCP.	29%	43%	29%	0%
37	Current evidence does not indicate that GH therapy increases the risk of craniopharyngioma recurrence. However, in the presence of active disease (radiologically evident progression), GH therapy should be withheld. Reinitiation may be considered after MDT discussion once the disease is stable (confirmed by two consecutive MRI scans showing no progression at 3- to 6-month intervals).	45%	33%	21%	0%
38	In patients with gonadotropin-deficient pediatric craniopharyngiomas, it is recommended that puberty induction therapy be initiated at the age of physiological puberty, usually 11-13 years for girls and 12-14 years for boys. During induction, the development of secondary sexual characteristics, progression of bone age, and rate of height growth should be closely monitored, and psychosocial adjustment should be regularly assessed. Follow-up visits every 3-6 months are recommended.	50%	32%	18%	0%
39	Acute intracranial pressure increase caused by hydrocephalus should be treated with emergency extraventricular drainage and active management of the primary tumor. Ventricular changes should be closely monitored after tumor resection.	66%	17%	17%	0%
40	It is recommended that all children with craniopharyngiomas complete a baseline vision assessment within 4 weeks of diagnosis. If visual deficits are identified, testing should be repeated 4-6 weeks after the initial surgical intervention. Comprehensive preoperative ophthalmic evaluation, intraoperative preservation of visual function, and regular postoperative monitoring of visual acuity changes are recommended.	56%	35%	9%	0%
41	Preoperative assessment, meticulous surgical techniques, and long-term rehabilitation management to mitigate the impact of craniopharyngioma on children's cognitive function.	71%	26%	3%	0%
42	Staged, individualized nutritional management of children with craniopharyngioma.	63%	29%	9%	0%
43	Management of hypothalamic obesity in children after craniopharyngioma surgery requires a multimodal, integrated intervention strategy that focuses on abnormal appetite regulation and impaired energy metabolism due to hypothalamic injury.	56%	32%	12%	0%
44	It is recommended that all pediatric craniopharyngioma cases, especially complex cases (e.g., large tumors, severe hypothalamic involvement, recurrence, or with significant complications) should be managed throughout the process by a multidisciplinary team (MDT). The multidisciplinary team should include specialists in neurosurgery, pediatric oncology, endocrinology, radiation oncology, ophthalmology, neuroimaging, neuropathology, nutrition, psychology, and rehabilitation to ensure comprehensive, multi-stage and individualized treatment.	71%	23%	6%	0%
45	The treatment strategy needs to be individualized according to the characteristics of the lesion, and intracapsular drug injection, craniotomy, endonasal endoscopic approach, and pharmacological treatment may be considered.	43%	43%	14%	0%
46	Participation in clinical trials is recommended for relapsed refractory cases.	26%	20%	51%	3%
47	Based on the principle of protecting hypothalamic function, surgery, radiotherapy and drug therapy are selected according to the specific situation. Severe hypothalamic complications require systematic and individualized management measures.	51%	34%	14%	0%
48	Postoperative follow-up should include: (1) imaging of the sellar and hypothalamic regions; (2) endocrine assessment throughout growth and development; (3) comprehensive neuropsychological testing (intelligence, memory, executive function) at 1 year; and (4) visual acuity, visual field, and fundus examination. All follow-up should be guided by a multidisciplinary team.	49%	37%	14%	0%
49	High-risk features such as age of onset <5 years, tumor diameter ≥ 4 cm, hypothalamic invasion/tight adhesions, multicompartmental growth, or associated hydrocephalus/	40%	37%	23%	0%

(*continued on next page*)

Table 2 (*continued*)

Recommendation	Contents	Highly recommended (%)	Recommend (%)	Agree (%)	Disagree (%)
	intracranial hypertension are recommended as core indicators for assessing the risk of recurrence and surgical complexity.				
50	It is recommended that the Ki-67 proliferation index be routinely recorded in the pathology report and used in conjunction with tumor volume and extent of resection as a reference for recurrence risk assessment.	59%	26%	12%	3%
51	Routine postoperative assessment of whether total resection has been achieved is recommended, and the next step of treatment should be assigned as early as possible in cases of incomplete resection, in order to reduce the rate of tumor recurrence and to improve the patient's prognosis.	71%	26%	3%	0%
52	If the cystic component of the tumor is predominant, intracapsular therapy (e.g., interferon) may be combined, but close monitoring for recurrence is required.	12%	26%	50%	12%
53	In children (<5 years of age) who are younger and whose tumor has not been completely resected, radiotherapy may be delayed until the tumor has progressed or until age >5 years if the residual lesion is stable, in order to reduce the risk of cognitive impairment.	31%	40%	23%	6%
54	A multifactorial clinical prognostic scoring model may be developed and prospectively validated to support recurrence-risk assessment and follow-up planning in pediatric craniopharyngioma. Such a model should be used only as an adjunct to MDT-based individualized decision-making, not as a standalone basis for treatment selection.	34%	43%	20%	3%
55	Validation of the validity and applicability of this scoring model in a multicenter prospective cohort and exploration of the potential for individualized treatment guided by other molecular markers is encouraged.	43%	34%	23%	0%

constraints, and tumor immune microenvironment features. Accordingly, suspected PCP in children should prompt confirmation of BRAF V600E status by immunohistochemistry or sequencing, and management should be discussed by an experienced MDT with attention to the balance between surgery, radiotherapy, and targeted therapy [17,19].

2.2. Pathogenesis

The hallmark molecular alteration in ACP is a missense mutation in exon 3 of the *CTNNB1* gene, leading to β-catenin stabilization, nuclear translocation, and constitutive activation of the Wnt/β-catenin pathway [20]. Despite sharing a scommon driver mutation, ACP shows considerable clinical and morphological heterogeneity [20,21]. This discrepancy between “relatively homogeneous molecular alterations” and “complex and variable clinical behaviors” has prompted an in-depth study of the molecular heterogeneity of ACP. In recent years, the research approach has shifted from focusing on single gene mutations to integrated multi-omics analyses in an attempt to establish a more precise molecular typing system. Multiple molecular subtypes of potential clinical significance have been proposed, laying the foundation for understanding the complex biology of ACP and exploring individualized therapeutic strategies [22]. In contrast, PCP exhibits a relatively well-defined and stable molecular profile, with the *BRAF V600E* mutation present in almost all cases [3,18,23]. This mutation leads to a conformational change in BRAF kinase, causing continuous activation of the downstream RAS-RAF-MEK-ERK (MAPK/ERK) signaling pathway, promotes cell proliferation and survival, and inhibits apoptosis. Continuous activation of this signaling axis may also affect the tumor immune microenvironment and therapeutic sensitivity, making it an important targets for molecular targeted therapy [24].

2.3. Course of the disease

More than 95% of craniopharyngiomas have a suprasellar component. Pure suprasellar tumors account for 20–41% of cases, combined supra- and intrasellar tumors for 53–75%, and purely intrasellar tumors for only 5–6%. In children, suprasellar craniopharyngiomas may extend into the anterior (9%), middle (8%) or posterior (12%) cranial fossa. Craniopharyngiomas typically grow slowly, with insidious onset of symptoms often lasting over a year before diagnosis [9,25–27]. Untreated, tumor progression can lead to increased intracranial pressure, visual field abnormalities, endocrine abnormalities (e.g. growth retardation, diabetes insipidus), neuropsychological changes, cognitive decline and seizures [9].

Pediatric craniopharyngioma is, in essence, a chronic disease with long-term, progressive health consequences, rather than a purely acute surgical tumor. Therefore, treatment goals should extend beyond short-term tumor control and focus on improving long-term quality of life and functional outcomes.

Tumors at diagnosis are often larger in children than in adults [21]. Larger tumor size is associated with higher rate of postoperative residue, shorter progression-free survival, and increased risk of recurrence [27]. Younger age at diagnosis (<5 years) and concomitant hydrocephalus are also associated with higher recurrence risk [28]. Postoperative diabetes insipidus as a negative prognostic factor for both recurrence and mortality [9]. While diabetes insipidus has prognostic value, postoperative epilepsy and electrolyte disturbances—particularly hypernatremia—carry greater prognostic significance.

Recommendation 1. Children presenting with headaches, visual impairment, or endocrine abnormalities (e.g. growth failure, diabetes insipidus) should undergo prompt neuroimaging (CT/MRI) to facilitate early diagnosis and intervention (Level of evidence: Moderate; Strength of recommendation: Strong).

[Basis and description]: This recommendation is based on numerous observational clinical studies and expert consensus. The causal relationship between symptoms and tumor is clear, and early imaging is the gold standard for diagnosing sellar region masses. Though lack of evidence from randomized controlled trials (RCTs) (ethical constraints), the clinical necessity and benefit are significant, so the strength of recommendation is“Strong”.

Recommendation 2. Prognostic evaluation should include age, presence of hydrocephalus, and postoperative diabetes insipidus. (Level of evidence: High; Strength of recommendation: Strong).

[Rationale and description]: Several large-sample retrospective cohort studies have confirmed[9,27] that young age (<5 years) and the presence of hydrocephalus at the time of initial diagnosis are high-risk factors for recurrence. Permanent postoperative diabetes insipidus is associated with hypothalamic injury and intraoperative pituitary stalk disruption and is a significant predictor of long-term mortality and reduced quality of life. The evidence is from high-quality observational studies and is therefore graded as “High”.

2.4. Clinical manifestations

Clinical symptoms of craniopharyngioma in children are mainly related to the location, size and shape of the tumor. Common manifestations include signs of elevated intracranial pressure (headaches, nausea, vomiting), often present as the initial symptoms [29]. Infants may present with macrocephaly [30]. Visual disturbances occur in over half of patients, including bitemporal hemianopsia from chiasmal compression [31]. Hypothalamic-pituitary defects are present in 80-90% at diagnosis, though only 15% initially present with endocrine symptoms, leading to diagnostic delay. Common deficiencies include growth hormone (>75%), gonadotropins (85%), thyrotropin (2–25%), and ACTH (25–70%). Diabetes insipidus is present in 9–38% of craniopharyngioma patients [32,33]. Hypothalamic obesity, behavioral changes, and cognitive dysfunction are also frequent [32].

3. Diagnostic workup

Diagnosis relies on clinical, imaging, and postoperative histopathological findings (see Fig. 2).

3.1. Radiographic examination

3.1.1. Indications for CT examination and assessment points (Fig. 3)

CT examination has an irreplaceable role in the diagnosis of pediatric craniopharyngioma:

Main indications:

Calcification detection: CT scanning (including bone window) can accurately identify tumor calcification (detection rate 45%-57%), especially the characteristic 'eggshell-like calcification' of ACP [34,35].

Bone assessment: clearly shows changes such as enlargement of the pterygoid saddle and bone erosion [36].

Emergency Situation: Pediatric patients are prone to hydrocephalus; CT provides rapid assessment.

MRI Contraindications: Such as implanted cardiac pacemakers.

Image Characteristics:

Density characteristics: the density of the cystic part is higher than that of the cerebrospinal fluid and lower than that of the normal brain tissue; the density of the cystic part shows different densities depending on the composition and content of the cystic fluid proteins, which are mostly low-density and may also show isodensity and hyperdensity.

Calcification manifestations: typical calcifications are seen in about half of the cases.

Bone window assessment: a key basis for surgical access selection.

Tumor enhancement: Enhancement of the parenchymal part of the tumor is usually closely related to the pituitary stalk, and enhancement of the tumor capsule wall may occur.

3.1.2. MRI examination techniques and assessment points

MRI is the modality of choice for delineating tumor extent, cystic components, and relationships with neurovascular structures [10]. The FLAIR sequence can effectively suppress cerebrospinal fluid signals, thereby enhancing the visualization of lesion boundaries adjacent to the ventricles or subarachnoid space, as well as peritumoral edema (such as hypothalamic hyperintensity), which is not achievable with T2WI.

Recommended sequences include T1WI, T2WI, FLAIR, DWI, and contrast-enhanced T1.

High-resolution 3D sequences (e.g., MPRAGE) can improve visualization of the pituitary stalk and hypothalamus.

MRI evaluation points(Fig. 3):

Tumor characteristics: Evaluate the tumor volume, morphology, cystic/solid ratio, and relationship with normal structures such as the peripheral optic chiasm and the third ventricle. The cystic component of the tumor has various imaging manifestations depending on the protein content and composition of the cystic fluid. Keratin-rich cystic fluid has a low signal on T2WI, while high-protein cystic fluid has a high signal on T1WI, and both cystic fluid signals suggest the diagnosis.

Calcification detection: Calcified foci tend to appear as areas of signal loss on MRI, but are less sensitive than on CT.

Tumor enhancement: Enhancement of the parenchymal part of the tumor is usually closely related to the pituitary stalk, and enhancement of the tumor capsule may occur.

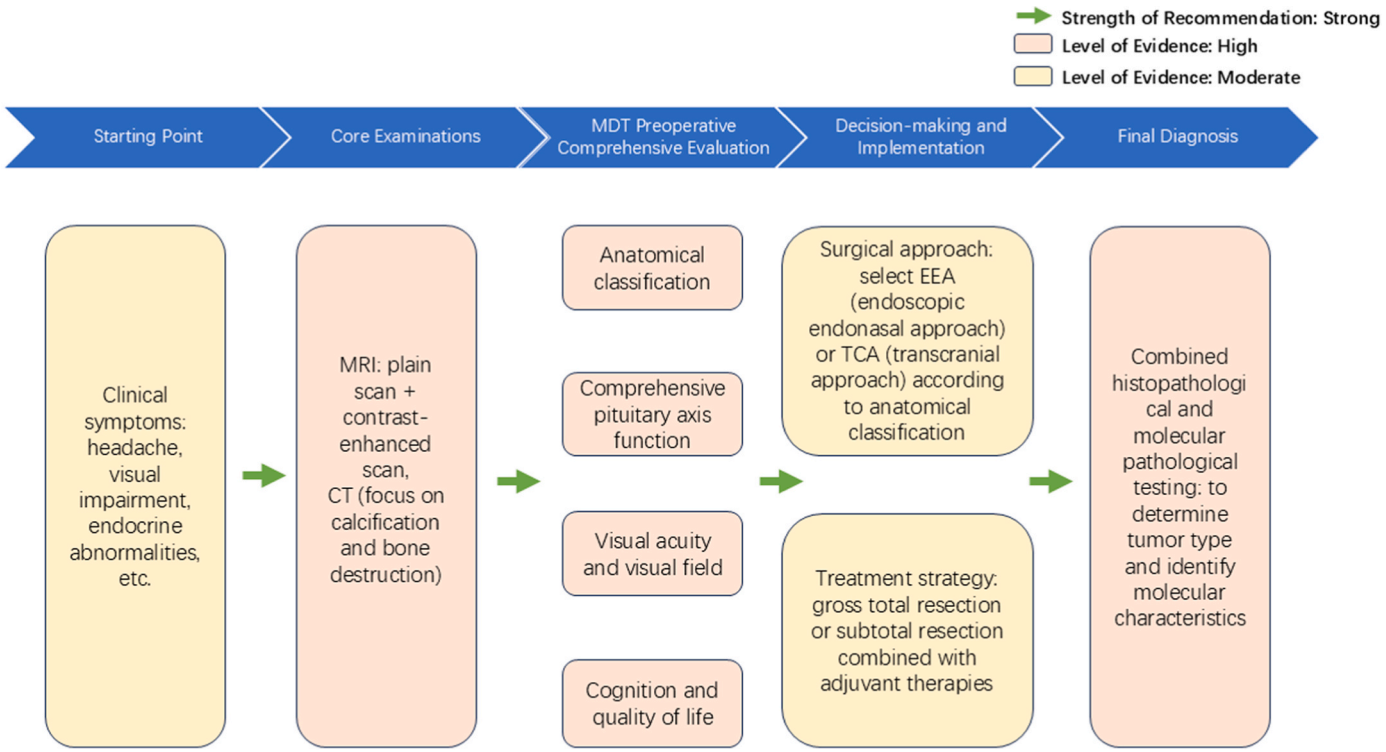
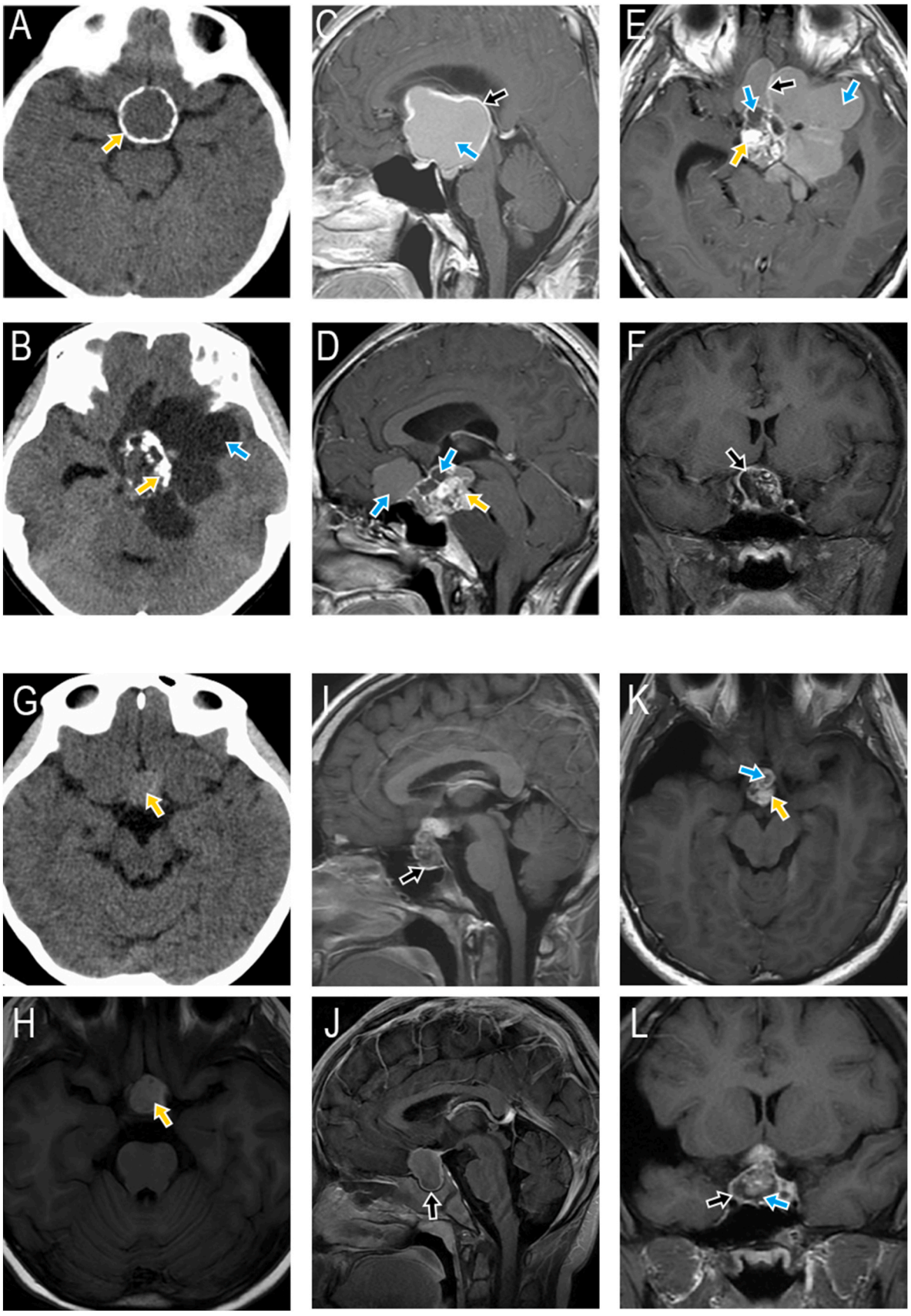


Fig. 2. Diagnostic and evaluation process for craniopharyngioma in children.



(caption on next page)

Fig. 3. Imaging of craniopharyngioma in children (A-F/ACP; G-L/PCP).
A: CT shows eggshell-like calcification of ACP (yellow arrow).
B: CT shows a large cystic lesion of ACP with nodular calcification (yellow arrow) and hypointense cystic component (blue arrow).
C: Sagittal T1 enhancement shows an ACP cystic lesion protruding into the third ventricle (blue arrow), with cyst wall enhancement (black arrow).
D: Sagittal T1 enhancement shows an ACP cystic-solid lesion (cystic component: blue arrow; solid portion: yellow arrow).
E: Axial T1 enhancement showing mixed cystic and solid lesion of ACP (cystic wall: black arrow; cystic component: blue arrow; solid portion: yellow arrow).
F: Coronal T1 enhancement of ACP mixed cystic and solid lesion with cystic wall enhancement (black arrow).
G: CT shows solid lesion of PCP (yellow arrow).
H: Axial T1 shows a solid lesion of PCP (yellow arrow).
I-J: Sagittal T1 enhancement of PCP mixed cystic and solid lesion with cystic wall enhancement (black arrow).
K: Axial T1 enhancement of PCP mixed cystic and solid lesion (cystic component: blue arrow; solid part: yellow arrow).
L: Coronal T1 enhancement showing PCP mixed cystic and solid lesion (cystic component: blue arrow; cystic wall: black arrow).

DWI, the parenchymal part of the tumor usually has no diffusion restriction and is low signal on DWI.

Vascular assessment: If the tumor extends parasellarly or laterally, or if it is adjacent to major blood vessels of the Circle of Willis (e.g. internal carotid artery, anterior/middle cerebral arteries), it is recommended that magnetic resonance angiography (MRA) be added to clarify the spatial relationship between the tumor and the blood vessels, and to assist in surgical planning.

Key Observation Indicators:

Relationship of the tumor to surrounding structures: focus on assessing whether the tumor involves the hypothalamic-pituitary axis, the optic crossings, and whether it extends into the third ventricle or the chiasmatic cistern.

Signs of hypothalamic involvement: Hypothalamic high signal on T2/FLAIR sequences may suggest edema or tumor infiltration; other common manifestations include mammillary body involvement, pituitary stalk deviation and optic chiasm displacement.

The value of enhancement scanning: it helps to identify areas of mass-like enhancement in the cystic wall or tumor parenchyma and determine the interface relationship between the tumor and the arachnoid cisterns in conjunction with vascular filling, which provides a basis for surgical access selection and risk assessment.

Recommendation 3. Preoperative CT should be considered for evaluating calcification and bony anatomy, particularly for ACP or when evaluating transsphenoidal surgical approaches. Non-contrast CT is the first-line modality in emergencies (e.g., acute hydrocephalus or herniation) for rapid assessment. Contrast-enhanced CT is indicated for tumor characterization if MRI is contraindicated. However, if MRI has clearly defined the tumor characteristics and none of the above indications (calcification assessment, surgical planning for transsphenoidal approach, or emergency setting) are present, CT is not mandatory. (Level of evidence: High; Strength of recommendation: Strong)

Recommendation 4. MRI is the preferred imaging modality for pediatric craniopharyngioma due to superior soft tissue resolution, which is critical for surgical planning (Level of evidence: High; Strength of recommendation: Strong).

[Rationale and description]: CT is superior to MRI in showing calcification (a common feature of ACP) and bone structure, and is essential for the planning of transsphenoidal surgical access. This recommendation is based on the characteristics of imaging technology and a large amount of clinical practice experiences. Although there is no RCT comparison, the clinical value is widely recognized, so the level of evidence is “High” and the strength of recommendation is “Strong”.

3.2. Endocrine evaluation

A comprehensive evaluation of hypothalamic-pituitary function is essential. Baseline tests should include serum electrolytes, blood and urine osmolality (to screen for diabetes insipidus), thyroid function (TSH, free T4), adrenocorticotropic hormone (ACTH) and cortisol (morning/evening), gonadotropins (LH, FSH) and sex hormones, growth hormone, and IGF-1 and prolactin [37]. Record blood sodium and urine specific gravity to assess water and electrolyte balance. For developing children, height and weight standard deviation scores and bone age should also be measured and growth rate analyzed; refer to endocrinology promptly if abnormality is found.

If the basic tests suggests hormonal abnormalities, further dynamic provocation or suppression tests may be needed. Commonly used tests include: insulin tolerance test or ACTH stimulation test to assess adrenal function; arginine, glucagon, clonidine and other stimulation tests to assess growth hormone secretion; GnRH stimulation test to assess gonadal axis function; TRH stimulation test for thyroid axis function. These tests help to detect occult hormone deficiency and guide postoperative hormone replacement and growth management.

Based on the study by van Santen et al. comprehensive assessment of hypothalamic function should include the following domains: body weight/BMI, appetite changes, thirst/fluid intake rhythm, thermoregulation, sleep-wake cycle, and mood and behavior.

For endocrine evaluation, baseline hormone levels represent the minimum acceptable standard, whereas dynamic provocation tests represent the ideal (gold standard) assessment.

Recommendation 5. Systematic pre- and postoperative assessment of hypothalamic-pituitary function is recommended and should be conducted by an experienced pediatric/pituitary endocrinologist in a dedicated pituitary center or MDT setting. Dynamic testing should be used as clinically indicated. (Level of evidence: High; Strength of recommendation: Strong).

3.3. Cognitive, behavioral and quality of life assessment

Cognitive evaluation should include executive function, memory, attention, and intellectual ability [38]. Focus on executive functioning (BRIEF scale or DKEFS test recommended), memory functioning (CVLT-C or WMS scale), and attention (Conners Continuous Performance Test). Intelligence tests (WISC-V/WPPSI-IV) can be secondary reference indicator. Visual/verbal memory and attention tests may be supplemented as necessary. Incorporating neurocognitive monitoring into routine follow-up helps assess outcomes and guide individualized rehabilitation.

Behavioral and emotional assessment: Monitor for behavioral and emotional changes pre- and post-operatively. Scales such as the Child Behavior Checklist (CBCL) can evaluate attention deficit, hyperactivity, mood disorders and social adjustment. This aids early identification of ADHD, anxiety, or depression for timely intervention.

Assessment of quality of life: Quality of life is an important endpoint in follow-up management. Questionnaires such as the Pediatric Quality of Life Scale (PedsQL) are recommended to assess physical, psychological and social functioning [39]. Studies using PedsQL and neuropsychological assessment has been studied and found that cognition and social adjustment may be affected. Regular assessment of quality of life and psychological status may provide a basis for the multidisciplinary team to develop supportive therapeutic and educational interventions.

For cognitive assessment, brief screening represents the minimum

acceptable standard, whereas comprehensive neuropsychological testing represents the ideal (gold standard) assessment.

Recommendation 6. Neuropsychological and cognitive assessments should be performed before and after surgery, as well as during long-term follow-up, using culturally appropriate tools. These should be integrated into long-term follow-up. (Level of evidence: Moderate; Strength of recommendation: Strong)

[Rationale and description]: Hypothalamic involvement and the treatment itself (surgery/radiotherapy) can lead to cognitive deficits [38]. Standardized assessment quantifies impairment and guides rehabilitation. The evidence is mainly from observational studies and cohort follow-up, so the level of evidence is "Moderate". The strength of recommendation is "Strong", given the significant impact on quality of life.

3.4. Ophthalmologic evaluation

Visual acuity: All patients should have a detailed visual acuity examination, including uncorrected and corrected vision. School-age children can be evaluated with Snellen's attempt charts, and younger children can be evaluated with Lea's symbols or a pointing visual acuity chart. Record eye alignment and refractive error; refer for corrective lenses if needed. Abnormal vision (e.g., blurriness, insensitivity to light) suggests optic nerve involvement and requires careful monitoring.

Visual field examination: tumors in the sellar region often cause visual field defects, such as bitemporal hemianopsia. Formal perimetry should be performed: automated static visual fields (Humphrey, Octopus, etc.) or Goldmann's kinetic perimetry for school-age children, and confrontation, tangent screen, or visual evoked potentials for preschool children to assess the extent of visual field defects. Visual field examination quantifies the extent of damage and provides an objective index for preoperative localization and postoperative outcome assessment.

Fundoscopy should be performed preoperatively and at each follow-up visit to look for edema or atrophy of the optic disc. Disc edema suggests increased intracranial pressure, and pallor or blurred margins suggests chronic optic nerve compression. Retinal and optic nerve lesions may also reflect the effects of tumors or surgical complications on visual pathways.

For ophthalmologic evaluation, visual acuity and fundoscopy represent the minimum acceptable standard, whereas formal perimetry represents the ideal (gold standard) assessment.

Recommendation 7. A comprehensive ophthalmologic evaluation is recommended for all patients at diagnosis and during follow-up. (Level of evidence: High; Strength of recommendation: Strong)

3.5. Differential diagnosis

The differential diagnosis of craniopharyngioma in children needs to be based on a thorough clinical assessment and multimodal imaging, which is recommended to be determined through a multidisciplinary team (MDT) discussion. MDT discussion: A fixed team consisting of specialists from neurosurgery, pediatric endocrinology, radiation oncology, neuroimaging, ophthalmology, pathology, nutrition, psychology, and rehabilitation, which regularly conducts joint case discussions and collaboratively develops individualized treatment plans. Sellar region lesions that need to be differentiated can be classified into the following three categories.

(1) Other sellar region tumors
   1) Optic nerve/optic cross glioma
      Imaging features: T2 high signal lesion with uneven enhancement along the optic nerve pathway.
      Typical presentation: enlargement or distortion of the optic nerve
      Clinical features: progressive vision loss
   2) Germ cell tumors
      Prevalent population: children and adolescents
      Typical presentation: enhancing solid nodule with restricted DWI diffusion, elevated serum AFP/β-HCG (diagnostic value); teratoma can be seen as a mixed component of fat and calcification; imaging features: inhomogeneous signals on MRI, fat-suppressed sequences are of discriminatory value.
   3) Hypothalamic hamartoma
      Preferred age: infants and young children.
      Clinical manifestations: precocious puberty, gelastic epilepsy, and other seizures.
      Imaging features: located between mammillary bodies and infundibulum; signal similar to grey matter; no enhancement; no signs of tumor growth.
   4) Chordoma
      Origin: notochord remnant tissue
      Imaging manifestations: CT suggests bone destruction and speckled calcification; MRI shows T2 high signal and significant enhancement; origin from bony structures.
      Differential points: location and imaging similar to craniopharyngioma
      Other rarer tumors of the sellar region, such as pituitary adenomas, meningiomas, metastases and lymphomas, are extremely rare in children and are generally not used as a routine differential diagnosis, although vigilance is still required in atypical cases.

(2) Non-neoplastic sellar region lesions
   1) Rathke's cyst: originated from the remnants of Rathke's cyst; imaging features: unilocular cystic lesion, thin-walled and smooth without enhancement, cystic fluid signal performance is variable depending on the protein content; clinical presentation: mostly asymptomatic, or accompanied by headache and hypopituitarism.
   2) Hypothyroidism-associated pituitary hyperplasia: pituitary basophilic hyperplasia due to elevated TSH levels. Imaging shows symmetrical soft tissue thickening in the sellar with homogeneous enhancement; diagnosis based on: low T4, high TSH levels.
   3) Arachnoid cyst: congenital cystic lesion, CT hypodense, MRI shows T1 low signal, T2 high signal (isosignal with cerebrospinal fluid), clear borders without enhancement.
   4) Dermoid/epidermoid cysts: dermoid cysts show high signal in T1WI, mixed signal in T2, high signal in DWI due to lipid content, and may contain fat and calcification; epidermoid cysts show low/equal signal in T1, high signal in T2, high signal in DWI in MRI, and there is no enhancement of dermoid/epidermoid cysts in contrast scan.

(3) Inflammatory and infiltrative lesions
   1) Langerhans cell histiocytosis: most common in children, may invade the saddle region and pituitary stalk, manifested as thickening and enhancement of the pituitary stalk, often combined with central diabetes insipidus, DWI is helpful in differentiating from tumors.
   2) Nodular disease: multi-systemic involvement, with thickening of the pituitary stalk and nodular enhancement in the sellar region; the diagnosis is based on multiaxial pituitary hypoplasia, which needs to be combined with systemic manifestations and ACE levels.
   3) Tuberculous granuloma: imaging features are nodular enhancement, which may be accompanied by periampullary thickening or hydrocephalus; clinical signs of infection are often present, and CSF examination has auxiliary diagnostic value.

Recommendation 8. A standardized preoperative protocol including imaging, endocrine, visual, and cognitive assessments is recommended. A multidisciplinary team (MDT) discussion is encouraged for diagnostic accuracy and treatment planning. It is recommended that pediatric craniopharyngioma patients be referred to and managed within a Pituitary Tumor Center of Excellence (PTCOE)—a designated high-volume center providing a fixed multidisciplinary team, standardized care pathways, and 24-h endocrine and intensive-care support. This PTCOE model of centralized management extends beyond ad hoc MDT discussion and has been associated with higher rates of safe resection and better endocrine and functional outcomes. (Level of evidence: High; Strength of recommendation: Strong).

4. Treatment strategies

The treatment strategy includes surgical options, perioperative management, postoperative assessment and adjuvant therapy for residuals, management of recurrence, endocrine replacement, strategies for special cases, and follow-up/long-term management, as illustrated in the flowchart in Fig. 4.

4.1. Surgical treatment

Surgery is the first-line choice to alleviate symptoms and obtain histopathology. T Surgery is an important first-line treatment for pediatric craniopharyngioma to relieve mass effect, obtain histopathological diagnosis, and achieve tumor control. However, the goal of surgery should be maximal safe resection rather than mandatory gross total resection. In patients with clear hypothalamic involvement, particularly Puget grade 2 tumors, attempted gross total resection should be avoided when it is expected to cause additional hypothalamic, endocrine, visual, or neurocognitive morbidity. When radiotherapy is available and appropriate, planned subtotal resection followed by observation or adjuvant radiotherapy should be considered through MDT discussion. This is central to surgical treatment and crucial for long-term survival [40–42]. If total resection is difficult to achieve, subtotal resection combined with radiotherapy can be considered [43].

Surgical decision-making should be based on a comprehensive assessment of tumor anatomy, relationship to vital structures, child's overall health, and potential risks, including both short- and long-term risks.

4.1.1. Indications and contraindications for surgery

Indications: Cases with definitive imaging diagnosis (even if asymptomatic) or those presenting with tumor-induced deficits: Hydrocephalus from CSF pathway obstruction; Endocrine dysfunction (e.g., growth hormone deficiency, diabetes insipidus, precocious puberty); Hypothalamic dysfunction (e.g., abnormal weight gain, impaired thermoregulation). Also consider for recurrent or progressive lesions.

Contraindications: Children with severe systemic conditions (e.g., cardiopulmonary failure, coagulation disorders, active infection) unable to tolerate anesthesia/surgery; patients with very short life expectancy or advanced/terminal disease where surgery is unlikely to improve quality of life. For high-risk patients, consider aggressive adjuvant therapies (e.g., cyst drainage for large cystic tumors, stereotactic radiotherapy, or experimental drug therapy) to control tumor burden and potentially enable later resection.

Surgical decision-making should be based on a comprehensive assessment of tumor anatomy, relationship to vital structures, child's overall health, and potential risks. Staged surgery or individualized strategies may be used. An MDT (neurosurgery, pediatric endocrinology, neuroimaging, radiotherapy) is recommended to evaluate and plan surgery.

Recommendation 9. Surgical resection with histopathological confirmation is recommended for symptomatic patients or those with clear radiological evidence of craniopharyngioma. (Level of evidence: Moderate; Strength of recommendation: Strong)

Recommendation 10. Reoperation should be considered for recurrent or progressive tumors after risk assessment. (Level of evidence: Moderate; Strength of recommendation: Strong)

Recommendation 11. Gross total resection is not recommended for tumors with extensive hypothalamic involvement (Puget grade 2).

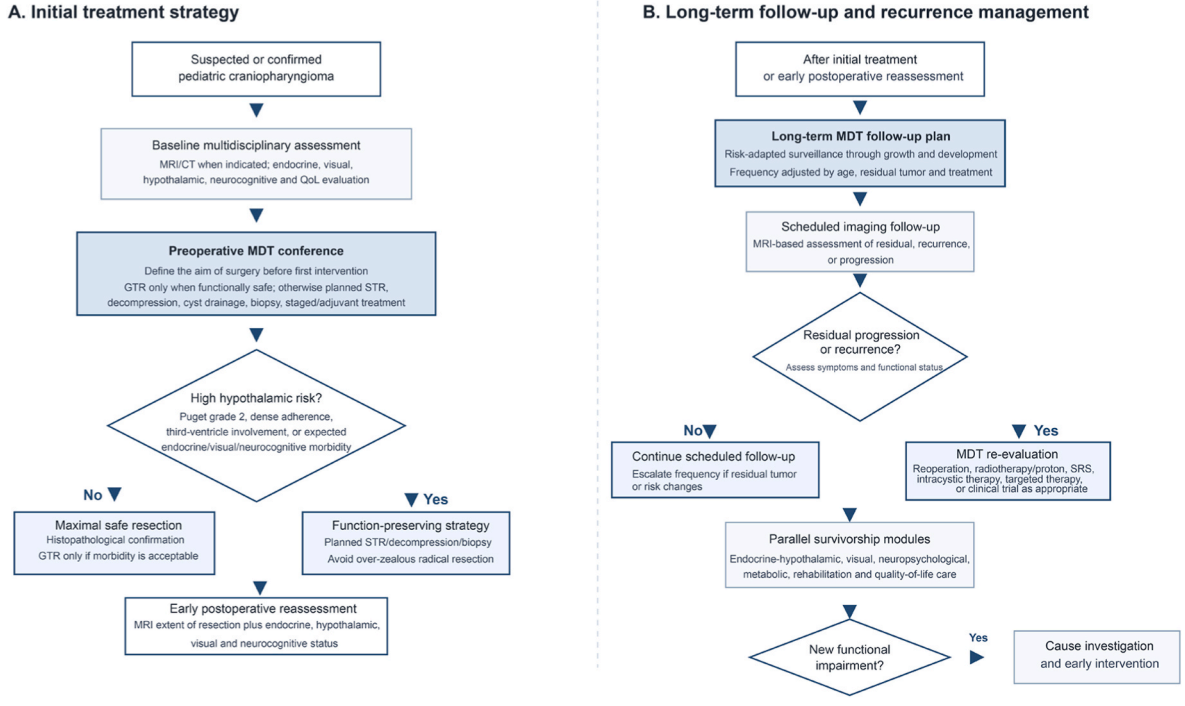


Fig. 4. Flowchart of treatment strategy and long-term follow-up management of craniopharyngioma in children.

Subtotal resection with radiotherapy is preferred to reduce severe complications. (Level of evidence: High; Strength of recommendation: Strong)

Recommendation 12. Surgery is not recommended for patients with severe medical comorbidities. Non-surgical options should be considered. (Level of evidence: Moderate; Strength of recommendation: Strong)

Recommendation 13. Preoperative adjuvant therapies (e.g., intracystic therapy) may be considered for high-risk or complex tumors to facilitate safer resection. (Level of evidence: Low; Strength of recommendation: Weak)

Recommendation 14. Treatment decisions should be made by an MDT. (Level of evidence: High; Strength of recommendation: Strong)

4.1.2. Surgical approaches

Depending on the anatomical location of the tumor, the two main surgical approaches currently used in clinical practice include the endoscopic endonasal approach (EEA) and the transcranial approach (TCA) [44]. Several grading systems guide approach selection.

(1) Puget grading [45]: Tumors are graded 0-2. Grade 0 tumor is confined to the sub-sellar diaphragm space and does not involve the hypothalamus, EEA is preferred; grade 1 tumor compresses but does not invade the hypothalamus, either EEA or open surgery can be considered; grade 2 tumor is poorly delineated from the hypothalamus and there is definite invasion, EEA needs to be chosen with caution [46–48], however, for surgeons with extensive experience in transnasal endoscopic surgery, the rate of total resection and quality of the surgery may be significantly better than TCA [44]. It is emphasized that for Puget grade 2 lesions, the surgical indications and extent of resection should be determined based on a combination of factors, including the extent of hypothalamic T2/FLAIR hyperintensity and the depth of tumor invasion into the third ventricle (e.g., whether the ependyma is breached), rather than considering surgery as an absolute contraindication.

(2) Kassam staging [49]: Type I tumors are classified as anterior funnel type, pushing the optic chiasm cross upwards and backwards, and can usually be approached by conventional EEA or a further extended trans-sellar node approach; Type II is a transfunnel tumor, which extends into the third ventricle, and similarly to Type I can be approached by EEA; Type III is a posterior funnel type, which invades the third ventricle upwards extends down toward pons; Type IV The tumor is mainly located in the third ventricle. All types except type IV can be operated with an extended EEA. Isolated third ventricle tumors are more amenable to craniotomy combined with transcallosal, transcortical or transventricular approaches.

(3) QST classification system: On the basis of the above typing, Professor Qi's team in China proposed the QST typing system based on the site of origin and growth pattern of the tumor [50]. This typing classifies craniopharyngiomas into Q, S and T types, revealing more precisely the primitive anatomical relationship between the tumor and the hypothalamic-pituitary axis, and providing an important “Chinese solution” for the individual selection of transnasal or craniotomy approaches. It should be emphasized that QST differs conceptually from displacement-based systems. Puget grading stratifies tumors by the degree of hypothalamic involvement/displacement [45], and the Kassam classification categorizes the already-grown tumor by its position relative to the infundibulum [49]; both characterize the tumor's secondary relationship to adjacent structures. In contrast, QST is defined by the anatomical site of origin along the hypothalamic–pituitary axis and the membranous barriers encountered there—Q (infradiaphragmatic/intrasellar origin), S (subarachnoid pituitary-stalk origin), and T (tuberal/third-ventricle-floor origin) [50]. Because the site of origin determines the tumor–hypothalamus and tumor–stalk dissection interface, QST may help predicts the achievable resection plane, the optimal corridor (EEA vs. TCA), and the likelihood of preserving hypothalamic–pituitary function in a way not fully captured by displacement-based systems [51]. Accordingly, in this guideline surgical strategy is individualized according to the combination of tumor origin/topography (QST), patient age, histological–molecular subtype (ACP vs. PCP/BRAF V600E status), and anticipated impact on quality of life, rather than tumor location alone. It should be emphasized that the Pascual-Prieto classification and the QST classification differ in their primary focus points and are therefore complementary rather than mutually exclusive. The Pascual-Prieto classification mainly focuses on the relationship between the tumor and the third ventricle floor, hypothalamic adherence, and hypothalamic involvement, which is useful for anatomical understanding and risk stratification. By contrast, the QST classification focuses on the presumed site of tumor origin, growth pattern, and the membranous barriers around the pituitary stalk, with the practical aim of guiding the choice between EEA and TCA. In China, the QST classification has been increasingly used in high-volume craniopharyngioma centers as a practical framework for individualized surgical planning.

Q-Type craniopharyngiomas originate under the saddle diaphragm and are tightly adherent to residual pituitary tissue, but their suprasellar portion is easier to peel off due to a multilayered membranous barrier. EEA allows direct management of the intrasellar-origin disease, preserving the residual glands and increasing the rate of total resection, which is significantly superior to TCA unless extreme bilateral suprasellar extension exists.

S-Type craniopharyngioma originates from the middle and lower pituitary stalk and is often confined to a single cerebral pool, which can well visualized by both EEA and TCA, but EEA can avoid operating in the neurovascular gap, which reduces the strain on the neurovascular vessels and is more advantageous in terms of visual preservation; when the tumor involves multiple cisterns or encases the important blood vessels, then TCA is safer.

T-type craniopharyngiomas originate from the distal part of the node and have a close relationship with the hypothalamus, so surgery needs to priorities the protection of the hypothalamus function. EEA reduces the risk of visual impairment and provides a direct, retraction-free ventral view of the tumor–hypothalamus interface; the choice between EEA and TCA for T-type tumors should therefore be guided by tumor geometry rather than by an inherent superiority of either route at the interface. In particular, when the main body of a T-type tumor grows upward and the posterior chiasmatic space is narrow, transnasal working space becomes limited and the optic chiasm is placed under greater strain. Therefore, for those with a wide posterior chiasmatic space and medium dilatation and elevation of the floor of the third ventricle, EEA is a suitable choice; while for those with a narrow posterior optic cross gap and extreme elevation and dilatation of the floor of the third ventricle, TCA via the trans-lamina terminalis approach is recommended to obtain a larger operating space and a better prognosis of hypothalamic function. At present, the QST staging system has been gradually recognized and applied by domestic and international colleagues. Conceptually, the QST and Pascual–Prieto systems are closely related, since both are origin- and topography-based and both center on the tumor–hypothalamus relationship. They differ mainly in their anchoring landmark and intended output: the Pascual–Prieto scheme is anchored on the third ventricle floor and the pattern of hypothalamic adherence and is used primarily for anatomical understanding and surgical-risk stratification, whereas QST is anchored on the membranous barriers encountered

along the pituitary stalk. Presenting the two frameworks together allows the origin-based logic of QST to be appreciated within the topographical context already familiar to international readers.

(4) In addition, in China, there is also Professor Hong, who specifically put forward the 'two types and three categories' for endoscopic operation [46,52].

4.1.3. Comparison of the two surgical procedures, EEA and TCA

Data from studies in adult patients showed that TCA and EEA were comparable in terms of the extent of tumor resection, while the incidence of cerebrospinal fluid leakage was higher in the EEA group [53,54]. However, it is worth noting that studies in pediatric patients suggest that EEA may have a higher rate of total resection and a lower rate of recurrence [55]. A Meta-analysis that included 22 studies further confirmed the superiority of EEA in improving visual prognosis and reducing recurrence rates, a finding that holds true in both adult and pediatric patients [56]. Despite the potential advantages of EEA, extra caution is needed in selecting the EEA surgical pathway for pediatric craniopharyngioma patients, especially for younger children under 5 years of age [57]. The characteristics of children in this age group are: 1) the development of the sphenoid sinus is often poor, with unclear anatomical landmarks and a high degree of dependence on the operator's experience and neuronavigation; 2) young children have a narrow nasal cavity and restricted intraoperative operative space, which requires the operator to have extremely proficient transnasal surgical skills; and 3) young children have poor postoperative compliance, and are susceptible to crying and restlessness, which requires solid skills in skull base reconstruction. Therefore, the applicability of EEA in children under 5 years of age should be carefully evaluated in clinical practice on the basis of fully weighing the risks and benefits to avoid irreversible adverse outcomes due to the inappropriate choice of operative modality.

4.1.4. Details and key points of surgical techniques

Craniopharyngioma resection requires special attention to the relationship between the tumor and the pituitary gland, pituitary stalk and hypothalamic tissue. Intraoperative injury to the posterior hypothalamus should be avoided as much as possible to avoid postoperative complications, such as hypothalamic obesity and neuropsychological disorders. In addition, the essential in surgical decision-making lies in the management of the pituitary stalk and hypothalamic protection strategies. Evidence suggests that sacrificing the pituitary stalk in pursuit of total resection will significantly increase the risk of hypopituitarism, but may not significantly affect on tumor recurrence rates [58]. Notably, the pituitary stalk often cannot be clearly visualized on preoperative imaging; in many cases its exact location and its relationship to the tumor only become apparent intraoperatively, typically after tumor debulking. Identification and preservation of the stalk should therefore rely on careful intraoperative exploration rather than on preoperative imaging alone. Accordingly, the pituitary stalk should be preserved whenever feasible, and sacrifice should be undertaken only when oncologically unavoidable and after weighing the substantial endocrine and quality-of-life consequences.

In the hands of experienced surgeons, for tumors of moderate size with relatively clear boundaries, en bloc or piecemeal resection may be attempted with adequate exposure and protection of critical structures (e.g., perforating arteries, pituitary stalk) to achieve gross total resection. For large tumors or those with tight adhesion to the hypothalamus, an intracapsular decompression and piecemeal resection strategy should be prioritized to maximize neurofunctional protection [59].

In determining the extent of surgical resection of craniopharyngiomas in children, total resection and the hypothalamus damage in cases with invasion of hypothalamus by preoperative image studies. Several large-sample retrospective studies and Meta-analyses have confirmed that total resection is superior to subtotal resection in improving overall and progression-free survival, and that subtotal resection may be associated with a risk of inadequate local control and deterioration of vision [60–64], In cases of hypothalamic involvement, subtotal resection combined with radiotherapy resulted in similar outcomes to total resection (5-year progression-free survival of 73% and 77%, respectively), while avoiding serious endocrine complications [61–63,65–67]. Among them, endocrine dysfunctions such as central diabetes insipidus and ACTH deficiency have been shown to be significantly associated with long-term mortality in patients with craniopharyngiomas [9,68]. However, it is worth mentioning that a number of high-level neurosurgical centers in China, on the basis of a profound understanding of the tumor-brain tissue interface (e.g., gliotic bands), are actively pursuing the "maximum safe resection with functional protection". Shi et al. show that [59], for experienced operators, even tumors involving the hypothalamus may still be completely resected by delicate microsurgical techniques with an acceptable functional prognosis. However, this strategy is highly dependent on the experience and skill of the operator and should only be implemented after a thorough evaluation by a multidisciplinary team in an experienced medical center [69]. Therefore, a comprehensive preoperative assessment of pituitary hypothalamic function is decisive for the development of an individualized surgical plan.

For tumors with a predominantly cystic component, for unilocular intraventricular cysts endoscopic marsupialization into the ventricle is prioritized to avoid Ommaya reservoir-related complications, while multilocular or complex cysts require individualized management (shunt vs. direct resection) [70,71]. Intermittent cystic fluid drainage with Ommaya reservoir implantation is an option in selected cases [62,63,65]. For complications, we recommend an individualized management strategy: for hydrocephalus due to craniopharyngioma cysts, priority should be given to cystic fluid drainage as an alternative to ventriculi-peritoneal shunt or external drainage; for large cystic-solid craniopharyngiomas with/without hydrocephalus, a two-stage procedure is recommended, with minimally invasive surgery to relieve increased intracranial pressure and intracranial pressure first, and supplemental neuroimaging assessment and multidisciplinary discussion to implement a definitive surgery. For surgeons with extensive surgical experience, a single tumor resection procedure can resolve the aforementioned issues.

Existing studies show significant differences in treatment outcomes and patient mortality rates for craniopharyngioma surgery performed by physicians with different levels of experience [72]. In view of the difficulty of surgery and the complexity of perioperative management of craniopharyngiomas, it is recommended that such patients should be centrally referred to medical centers with extensive experience in treating them. Ideally, the treatment of craniopharyngioma should involve an experienced multidisciplinary team with specialists in neurosurgery, endocrinology, radiotherapy, oncology, ophthalmology, imaging and pathology. This centralized, multidisciplinary and collaborative model of care is essential to ensure the best possible outcome for patients.

To assist clinical decision-making, the prognostic risk scoring model proposed in this guideline (see Table 4) can also be applied to surgical strategy formulation. For example, for patients in the **low-risk group (total score 0-2)**, if the tumor location is favorable, a more aggressive attempt at GTR may be considered. Conversely, for patients in the **high-risk group (total score $\geq$ 5)** (who typically present with risk factors such as age <5 years, Puget grade 2 hypothalamic involvement, and large tumor size), given the very high risks of both recurrence and surgical morbidity, the decision should favor function-preserving STR with proactive planning for postoperative adjuvant radiotherapy, rather than pursuing GTR at all costs.

Overall, pediatric craniopharyngioma should be treated in a specialized pituitary center with high case volume and a multidisciplinary team. For experienced surgeons, gross total resection should only be pursued when it is reasonable and safe. If intraoperative findings confirm tight adhesion between the tumor and the hypothalamic-

pituitary region, a subtotal resection strategy should be prioritized. Postoperatively, based on factors such as the child's age and residual tumor status, early adjuvant radiotherapy or deferred radiotherapy should be determined in discussion with radiation oncologists.

Recommendation 15. Surgery is recommended as the first-line treatment for craniopharyngioma in children, aiming at total tumor resection while preserving vital functional structures to improve overall and progression-free survival. The extent of resection should be individualized according to the degree of hypothalamic involvement, and gross total resection should not be pursued when it would compromise hypothalamic function (see Recommendation 11). (Level of evidence: High; Strength of recommendation: Strong).

Recommendation 16. The choice between EEA and TCA should be based on tumor anatomy, hypothalamic involvement, third-ventricle extension, surgeon experience, and MDT assessment, with the primary goal of maximizing surgical safety and functional preservation rather than maximizing the rate of total resection. (Level of evidence: Moderate; Strength of recommendation: Strong).

[Rationale and description]: These staging systems provide an objective basis for surgical access selection. Several retrospective studies have shown that individualized access based on typing improves resection rates and prognosis [50,73]. The evidence comes from non-randomized comparative studies and is therefore graded "Moderate".

Recommendation 17. Preserve the pituitary stalk whenever possible. If the tumor is densely adherent, prioritize stalk function with subtotal resection and radiotherapy over stalk sacrifice, which should only be a last resort due to increased long-term complications. (Level of evidence: Moderate; Strength of recommendation: Strong).

Recommendation 18. For tumors with definite involvement of the hypothalamus and demonstration of thalamic injury, if the surgeon assesses that total resection will result in further functional impairment, a strategy of subtotal resection combined with radiotherapy is recommended to ensure local control while reducing serious postoperative complications. (Level of evidence: Moderate; Strength of recommendation: Strong).

[Rationale and description]: Several retrospective studies have shown that subtotal resection + radiotherapy has a comparable long-term progression-free survival rate to total resection, but with fewer serious endocrine and neuropsychological complications [61–63, 65–67]. Due to the controversial nature of treatment choices and the trade-offs between different strategies, a strength of recommendation of 'moderate' is more appropriate, emphasizing individualized decision-making.

Recommendation 19. Comprehensive preoperative assessment of the functional status of the hypothalamus is recommended as a key decision-making basis for developing an individualized resection strategy. (Level of evidence: High; strength of recommendation: Strong).

Recommendation 20. It is recommended that for cystic predominant lesions or those with acute manifestations of intracranial hypertension, prior treatment with drainage of cystic fluid and reduction of intracranial pressure by drugs should be considered to alleviate acute symptoms and optimize the conditions for subsequent treatment. (Level of evidence: Moderate; Strength of recommendation: Strong).

Recommendation 21. It is strongly recommended that surgery for craniopharyngioma in children be performed by highly qualified and experienced neurosurgeons with the support of a multidisciplinary team. (Level of Evidence: High; Strength of recommendation: Strong).

4.1.5. Key points in perioperative management

(1) Perioperative use of dexamethasone to reduce peritumoral edema reduces postoperative neurosurgical mortality and is recommended for individualized assessment and rational use [74]. For those with pre-existing adrenal insufficiency, a stress dose of hydrocortisone may be more appropriate than dexamethasone. Postoperatively, the dose should be gradually reduced to a maintenance dose according to the condition of the patient until the functional integrity of the hypothalamic-pituitary-adrenal axis (HPA axis) is clarified [75].

(2) Management of electrolyte disturbances: perioperative water electrolyte management requires special attention to differentiate Central Diabetes Insipidus (CDI) from hyponatraemia. The typical triphasic response consists of CDI presenting 24-48 h postoperatively, followed by progression to the syndrome of abnormal secretion of antidiuretic hormone (SIADH) over the next 1-2 weeks, which may ultimately evolve into permanent diuresis. This reaction is particularly common in pediatric patients [76].

Cerebral salt-wasting syndrome (CSWS) can also occur at any stage of the perioperative period and may be associated with abnormal secretion of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) [77–79]. Its treatment is based on sodium supplementation and, if necessary, mineralocorticoid (e.g., fludrocortisone). Routine use of vasopressin receptor antagonists (e.g., tolvaptan) is not recommended to mask changes or exacerbate triphasic fluctuations.

For hyponatremia, potential causes such as CDI, SIADH, CSWS, central adrenal insufficiency and medical water load should be assessed together. Ambulatory monitoring of blood sodium, osmolality, and copeptin levels can help determine etiology and response to therapy. Particular attention should be paid to the fact that SIADH may occur as part of a triphasic response, while CSWS may occur in combination, which needs to be differentiated from clinical signs and laboratory parameters to prevent further neurological damage [43]. When managing hyponatremia or hypernatremia, fluctuating blood sodium levels may pose a greater risk than stable hyponatremia.

(3) Perioperative endocrine management: Children with craniopharyngiomas often have a combination of multiple pituitary hormone deficiencies in the perioperative period, and high priority needs to be given to the assessment and intervention of endocrine function. In children with preoperative hormone deficiencies, especially secondary adrenal insufficiency and hypothyroidism, hormone replacement therapy should be initiated preoperatively to reduce the risk of perioperative complications [35]. Hydrocortisone or prednisone is preferred for glucocorticoid replacement, and the dose should be individualized, with a physiological dose usually recommended for maintenance therapy preoperatively, and adjusted to a stress dose intraoperatively and postoperatively according to stress status. For thyroid hormone replacement, levothyroxine should be used, but it is important to assess and ensure adequate adrenal function prior to initiation to avoid adrenal crisis induced by thyroid hormone supplementation alone. Thyroid dysfunction is also a common postoperative complication, and studies have shown that up to approximately 85% of pediatric patients may require postoperative levothyroxine replacement therapy [80]. In addition, adrenocortical insufficiency occurs in more than 50 per cent of postoperative children, and the glucocorticoid dose should be adjusted according to body surface area, with a recommended dose of 6 to 9 mg/m^2 [81]. Systematic assessment of endocrine function should be carried out in the early postoperative period, and it is recommended to review thyroid function (FT4, TSH) and adrenal axis (ACTH, cortisol) related indexes in the first 1-2

weeks after the operation, in order to detect potential hormone deficiencies in a timely manner. Replacement therapy for anterior pituitary hormones should be individualized in accordance with the specific type of deficiency and clinical manifestations to ensure neurological recovery, growth and development, and quality of life of the child.

(4) Other issues: cases of acute onset combined with hydrocephalus may require external ventricular drainage, but caution should be exercised in the application of preoperative shunts, which may lead to narrowing of the ventricles of the brain and thus increase the operative difficulty of transventricular surgical access. Sympathetic storm is also an early and aggressive complication that should be given special attention in the postoperative period [82], and should be aggressively controlled with malignant hypertensive reactions, severe diabetes insipidus, and maintenance of circulatory and hydroelectrolyte stability to get through the critical phase under analgesic sedation and anesthetic intubation, if necessary.

Additionally, among the complications of surgery for craniopharyngiomas, the potential development of an internal carotid artery aneurysm exists. This primarily results from surgical instrument friction causing damage and thinning of the artery wall, leading to gradual protrusion. Regardless of the surgical approach, postoperative attention should be paid to cerebrovascular status, and for complex or repeat surgeries, cerebrovascular imaging is recommended to assess the patency of major arteries and anastomotic branches.

Given the high risk of perioperative water-electrolyte disturbances and endocrine crises in pediatric craniopharyngioma, surgery should be performed in a medical center capable of providing 24-h endocrinology specialist consultation and intensive care/high-dependency unit support.

Recommendation 22. Dexamethasone may be used perioperatively for cerebral edema. (Level of evidence: Moderate; Strength of recommendation: Strong)

Recommendation 23. Vasopressin receptor antagonists are not routinely recommended for hyponatremia due to risk of triphasic response. (Level of evidence: Moderate; Strength of recommendation: Strong)

Recommendation 24. Hyponatremia should be evaluated and managed based on etiology. (Level of evidence: Moderate; Strength of recommendation: Strong)

Recommendation 25. Polyuria should be evaluated for central diabetes insipidus and other causes. (Level of evidence: High; Strength of recommendation: Strong)

Recommendation 26. Preoperative correction of adrenal insufficiency and hypothyroidism is recommended. (Level of evidence: Moderate; Strength of recommendation: Strong)

Recommendation 27. Postoperative endocrine function should be assessed and managed long-term. (Level of evidence: High; Strength of recommendation: Strong)

4.2. Pathological diagnosis

Postoperative histological and molecular pathological diagnosis is the ultimate basis for confirming the diagnosis of craniopharyngioma. Minimum standard: For ACP, immunohistochemistry for nuclear accumulation of β-catenin; for PCP, immunohistochemistry for BRAF V600E mutation antibody. Gold standard: Molecular sequencing (e.g., Sanger sequencing or NGS) for detection of CTNNB1 and BRAF gene mutations.

ACP tends to be a mixed cystic-solid structure. The cystic fluid is dark green to brown in color and resembles motor oil in appearance [83]. It is often associated with secondary pathological changes such as calcification, fibrosis and cholesterol deposits [84]. The tumor is lobulated with an irregular surface and tightly adherent to surrounding structures. Histologically, well-differentiated epithelial tumor cells formed strands, lobules, bands, nodular swirls and irregular trabecular structures. The epithelial peripheral cells were densely arranged in a fenestrated pattern. Common degenerative changes include fibrosis, calcification, and anucleated squamous cell remnants forming nodular or swirling structures known as “wet keratin” [85]. Sparse microcystic areas of the stellate reticular layer were often intermingled with areas of dense wet keratin and tumor epithelium (Fig. 5C). The tumor protruded finger-like into the surrounding gliomatous brain tissue, and a large number of Rosenthal fibers were visible [86]. Another secondary degenerative change is a yellow granulomatous reaction of the contents of the ruptured capsule, which is characterized by cholesterol crystals, ferrous haemoflavin deposits, xanthomatous cells, multinucleated giant cells and lymphoplasmacytic infiltration [87]. Histological malignant progression of ACP is extremely rare and usually occurs only after multiple recurrences and radiotherapy, often decades after the initial diagnosis. The histological features of malignant progression may manifest as squamous cell carcinoma, enamel cell carcinoma or odontogenic carcinoma, but most cases lack specific histological features [88,89]. In terms of immunophenotype, tumor cells expressed p63 and cytokeratins such as 34βE12, CK5/6, CK7 and CK19. Unlike Rathke's cyst, ACP, PCP lacked CK20 expression [90]. PDL1 is expressed in cyst-lined tumor cells of ACP. SOX2 is expressed in only a small proportion of cells, whereas SOX9 is widely expressed [91]. An activating mutation in the *CTNNB1* gene is present in ACP. The mutation is clonal and present throughout the tumor epithelium; however, nuclear accumulation of β-catenin is spatially restricted to a small fraction of cells and is most pronounced in epithelial whorls (Fig. 5D). Ki-67 is usually found in fenestrated areas and is very poorly expressed in epithelial vortices [92].

PCP is largely characterized by solid or cystic-solid structures, and in a few cases it may also appear predominantly cystic; cystic structures are usually accompanied by cauliflower-like solid nodules [19]. The contents of the capsule often appear as a viscous yellow fluid. The tumor is usually non-calcified, well demarcated, spherical, with no obvious adhesion to the surrounding brain tissue, and papillary structures can be seen on the surface [17]. Histologically, PCP consisted of non-keratinised mature squamous epithelium overlying a fibrovascular axis, with no stellate reticular layer structure or wet keratin, and calcification was rare (Fig. 5A). Densely arranged cells were seen in the basal cell layer, but there was no significant fenestrated structure. The tumor was well demarcated from the brain parenchyma without infiltrative protrusions. Neutrophil infiltration was common within the tumor, and T cells and macrophages were also seen in the fibrovascular axis and tumor epithelium [11,93]. In up to 1/3 of cases, single or small clusters of PAS-positive cup cells are seen within the tumor cells, and in a few cases, ciliated epithelium is seen [13]. These histological features overlap with Rathke's cleft cysts with extensive squamous metaplasia. Histological malignant progression of craniopharyngiomas is extremely rare, but none of the currently reported cases of malignant progression have been tested for the BRAF p. V600E mutation. Immunophenotypically, p63 and cytokeratin 34βE12, CK5/6, CK17 and CK19 were positively expressed, but CK7 was expressed only in the superficial epithelium [94,95]. PDL1 is expressed in multilayered tumor cells around the fibrovascular axis. SOX9 is differentially expressed. Almost all PCPs have the *BRAF V600E* mutation, which can be detected in the tumor epithelium by mutation-specific antibodies (Fig. 5B), thus differentiating them from ACP and Rathke's cysts [3,18]. Ki-67 is usually expressed only in the basal layer of PCP.

Recommendation 28. Histopathological and molecular testing should be performed to guide diagnosis and treatment. (Level of evidence: High; Strength of recommendation: Strong)

[Rationale and description]: The 2021 WHO classification has

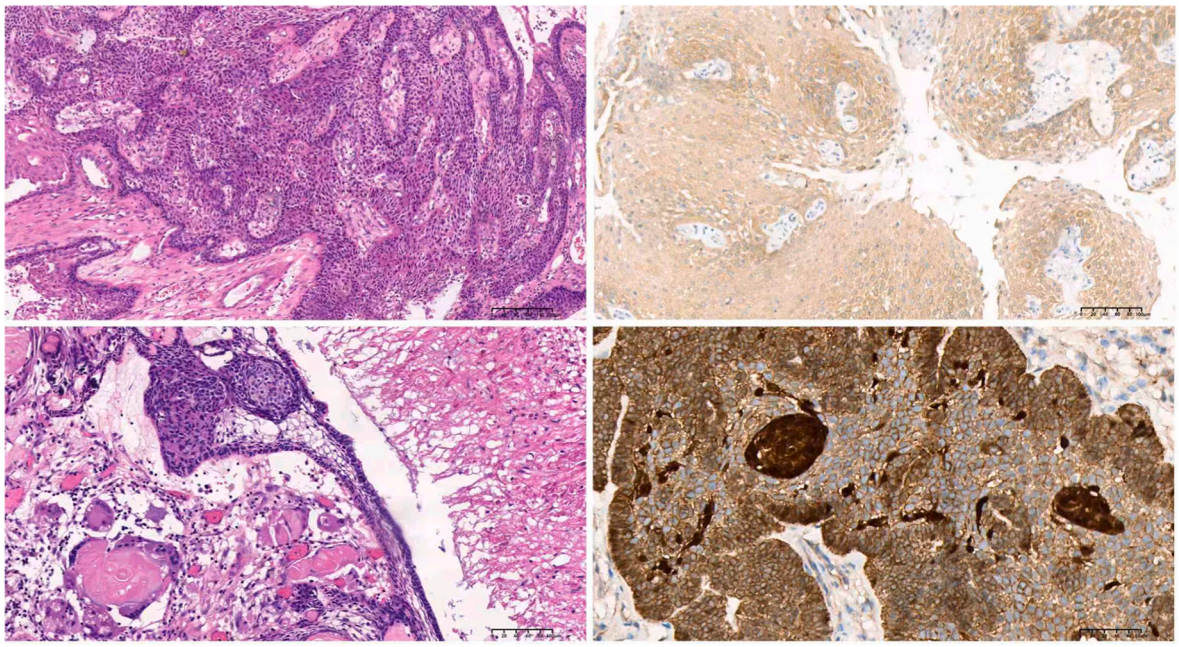


Fig. 5. Histopathological and molecular features of pediatric craniopharyngioma. (**A**) Papillary craniopharyngioma (PCP) showing non-keratinizing stratified squamous epithelium arranged around fibrovascular cores on hematoxylin and eosin (H&E) staining. (**B**) Diffuse cytoplasmic immunoreactivity for mutant BRAF V600E in PCP, detected by VE1 immunohistochemistry. (**C**) Adamantinomatous craniopharyngioma (ACP) showing peripheral palisading epithelium, stellate reticulum, and wet keratin on H&E staining. (**D**) Nuclear accumulation of β-catenin in epithelial whorls of ACP on β-catenin immunohistochemistry. Scale bars are shown in each panel.

classified ACP and PCP as two separate types of tumor with different molecular driver genes (*CTNNB1 vs BRAF V600E*) [7,18]. Molecular typing is not only the basis for accurate diagnosis, but also a prerequisite for guiding targeted therapies (e.g. BRAF inhibitors for PCP) [24]. In routine clinical practice, nuclear accumulation of β-catenin by immunohistochemistry is usually sufficient to support the diagnosis of ACP, whereas BRAF V600E immunohistochemistry is a practical screening method for PCP. Sequencing of CTNNB1 or BRAF should be considered when immunohistochemical results are inconclusive, histological features are atypical, or targeted therapy/trial enrollment is being considered, but it is not required as a routine test for every child. (Level of evidence: High; Strength of recommendation: Strong).

Recommendation 29. Histopathological diagnosis should be complemented by characterization of the defining driver alterations—CTNNB1 (ACP) and BRAF V600E (PCP). In routine practice, mutation-specific immunohistochemistry (nuclear β-catenin for ACP; VE1/BRAF V600E for PCP) is the minimum acceptable standard and is usually sufficient for diagnosis. Because immunohistochemistry detects the downstream protein change as a surrogate, definitive confirmation of the underlying mutation requires a molecular technique (Sanger sequencing or next-generation sequencing); this should be reserved for cases with equivocal immunohistochemistry, atypical histology, or when mutation confirmation is required for targeted-therapy eligibility or clinical-trial enrollment. (Level of evidence: High; Strength of recommendation: Strong).

4.3. Principles of radiotherapy

Radiotherapy includes a variety of technical options such as conventional radiotherapy and stereotactic radiotherapy (e.g., Gamma Knife). Radiotherapy segmentation can be by conventional segmented radiotherapy or stereotactic radiotherapy, and radiotherapy beams can be photon or proton rays.

Accessibility of radiotherapy resources in China should be taken into consideration when selecting treatment modalities. Conventional radiotherapy is accessible in most provincial cancer centers across the country. Stereotactic radiosurgery (Gamma Knife/CyberKnife) is available in major cities. Proton therapy centers are currently concentrated in a few first-tier cities (e.g., Beijing, Shanghai), with limited accessibility and high cost. Therefore, the choice of radiotherapy modality should be made based on a comprehensive assessment of the child's clinical condition, the family's financial situation, and local medical resources.

4.3.1. Indications for radiotherapy

(1) Conventional radiotherapy: adjuvant radiotherapy after subtotal resection (STR) achieves comparable control to GTR, with similar 5-year PFS (67-77% vs 69-73%) and reduced treatment-related complications [5,63,96–98]. Conventional radiotherapy after STR is the standard treatment strategy for adult craniopharyngiomas, and there is a lack of direct evidence to support the benefit of adjuvant radiotherapy after GTR [62,64,99]. Indications for radiotherapy of craniopharyngiomas in children should be strictly limited. It is mainly indicated for 1) postoperative residual or recurrent cases that are not suitable for reoperation due to high risk or patient's wishes, etc., and 2) older children (usually >8-10 years old) with residual tumors after multiple recurrent surgeries. Routine postoperative adjuvant radiotherapy is not recommended for craniopharyngiomas in children. This is mainly due to the potential long-term cognitive, endocrine, and growth effects of radiotherapy in developing children. Radiotherapy should also not be used as routine adjuvant therapy for craniopharyngiomas with predominantly cystic lesions after cyst drainage, except in patients who do not wish to undergo surgery or are in no condition to undergo surgery because of the limited responsiveness of cystic lesions to radiotherapy [20,100]. Re-irradiation of craniopharyngiomas that have progressed or recurred after initial radiotherapy may be a prudent option after a thorough assessment of the benefits and risks. The optimal timing of radiotherapy delivery (early postoperative adjuvant therapy or radiotherapy after tumor

progression) is not yet clear. Low-quality evidence suggests that radiotherapy after tumor progression may increase the risk of visual impairment and endocrine dysfunction (including central diabetes insipidus) in patients, but does not affect overall survival [101,102], whereas early postoperative radiotherapy may be beneficial in terms of better quality of survival and tumor control [102]. However, in pediatric patients, the long-term side effects of radiotherapy need to be particularly weighed against the benefits of tumor control. Modern conformal radiotherapy techniques, particularly proton therapy, may reduce radiation exposure to normal developing brain tissue and may be associated with more favorable neurocognitive outcomes in selected pediatric craniopharyngioma cohorts [103]. However, proton therapy is not uniformly available in China and is currently concentrated in a limited number of specialized centers, with additional considerations regarding cost and access. Therefore, proton therapy should be considered when available and clinically appropriate, but treatment selection should also account for local radiotherapy expertise, family preference, patient age, tumor location, residual disease status, and expected long-term functional outcomes.

(2) Stereotactic radiosurgery: in pediatric patients, Gamma Knife can also be used only for small residual or recurrent tumors and in patients who are generally poor surgical candidates [104,105]. There is no high-quality evidence comparing the efficacy of stereotactic radiosurgery with other radiotherapy techniques in the treatment of childhood craniopharyngiomas [106–108].

(3) Proton therapy: Proton therapy is capable of precisely controlling the depth of radiation and stops releasing most of the energy once it reaches the tumor site, thus significantly reducing the radiation exposure to surrounding healthy, developing tissues [103]. Relatively better dose distribution compared to photon rays, with dose distribution advantages for younger children and those with tumors close to key structures. Retrospective studies have shown no difference in overall or progression-free survival between proton beam therapy and conventional photon therapy, and a lower recurrence rate of cystic lesions with proton therapy [101]. In a prospective study of 94 children with a median age of about 9 years, patients treated with proton therapy showed better post-treatment preservation in cognitive function than those treated with photon therapy [103]. Comparison of different radiotherapy modalities is shown in Table 3.

Recommendation 30. For recurrent tumors, reoperation is an important option, but the risks and benefits should be carefully evaluated. If surgery is not suitable, radiotherapy or other adjuvant therapies may be considered. For residual tumors after subtotal resection, especially those at risk of (Tables 4 and 5) progression, postoperative adjuvant radiotherapy (under appropriate age and resource conditions) is an effective means of tumor control. (Level of evidence: Moderate; Strength of recommendation: Strong)

Table 4
Prognostic risk scoring factors and scoring.

Risk factor	Decision condition	Score
Clinical factor		
Age	≤5 years	2
Hypothalamic involvement (Puget level 2)	Yes	2
Maximum tumor diameter ≥4 cm	Yes	1
pathological factors		
Ki-67 ≥ 10%	Yes	1
Treatment-related factors		
Extent of excision	Incomplete excision	2
Adjuvant radiotherapy in patients with subtotal resection	Undone	1

Table 5
Prognostic risk stratification and management recommendations.

Risk stratification	Total Score Range	Key Management Strategies
Low risk	0–2	Regular follow-up, no need for routine postoperative radiotherapy; observation preferred in total resection patients, endocrine/imaging monitoring if necessary
Medium risk	3–4	Close monitoring; for residual/recurrent lesions, select reoperation or radiotherapy based on specific circumstances. If not suitable for surgery and older, consider adjuvant radiotherapy; regular MRI follow up; consider synchronous targeted drug therapy for BRAF mutations
High risk	≥5	MDT discussions at an experienced center are recommended to develop an intensive comprehensive treatment plan. Adjuvant therapy (e.g. radiotherapy, targeted, intracapsular therapy, etc.) is actively considered for residuals that cannot be completely resected, but decisions about radiotherapy in younger children need to be made with extreme caution.

[Rationale and description]: This is a key difference between the treatment strategies for children and adults with craniopharyngiomas. Priority is given to surgery and caution to radiotherapy in order to maximize protection of long-term function in children. This recommendation is based on the experience of a large number of pediatric cohort studies and an in-depth knowledge of the side effects of radiotherapy, and therefore the level of evidence is "Moderate" and the strength of recommendation is "Strong".

Recommendation 31. Radiotherapy modality and timing should be individualized (Level of evidence: High; Strength of recommendation: Strong).

Recommendation 32. Proton therapy may be considered to reduce radiation exposure to normal tissues. Proton beam therapy should be considered/prioritized for pediatric patients when available, to reduce integral dose to the developing brain. (Level of evidence: Moderate; Strength of recommendation: Strong)

Table 3
Comparison of radiotherapy modalities for craniopharyngioma in children.

Treatment	Typical indications	Typical Dosage and Segmentation Scenarios	Key Benefits	Potential complication
Conventional radiotherapy	Adjuvant therapy after STR; residual tumor progression	Total dose 50.4-54 Gy, single 1.8-2.0 Gy	Widely used and experienced	Endocrine dysfunction, neurocognitive dysfunction, visual impairment, delayed stroke and vascular malformations, secondary tumors
Stereotactic radiosurgery	Small, well-defined lesions; residual/tumor recurrence	12 Gy-14 Gy	Non-invasive, precise targeting of small lesions, minimising damage to surrounding tissue	New or exacerbated pituitary dysfunction may have lower rates of local control in pediatric patients than in adults
Proton therapy	Pediatric patients	Total dose 54 Gy (RBE), single 1.8 Gy	Significantly reduces radiation exposure to surrounding healthy, developing tissues	Lower incidence than conventional radiotherapy

4.3.2. Radiotherapy target area and dose

A non-randomized controlled study showed that reducing the edge of the clinical target area from 10 mm to 5 mm did not reduce patient survival (96.2% *vs* 88.1%) [109,110]. There are no randomized controlled trials comparing the differences in efficacy of various radiotherapy regimens in the treatment of craniopharyngiomas, which are generally delivered at a total dose of 50-54 Gy in 28-30 sessions [110–113]. A retrospective study suggests that irradiation doses below 54 Gy may be associated with increased tumor recurrence; however, clinical decision-making needs to be weighed against the balance between irradiation dose and the risk of visual optic chiasm-radiotoxicity [114]. CT/MRI should be performed periodically during treatment to ensure that the treatment plan adequately covers any cystic lesion progression. If coverage is found to be inadequate, the radiotherapy plan may need to be reformulated.

Recommendation 33. A CTV margin of 5 mm is recommended (Level of evidence: Low; Strength of recommendation: Weak)

Recommendation 34. Conventional radiotherapy doses of 50.4–54.0 Gy in 28–30 fractions are standard. SRS doses of 12–14 Gy may be used for small lesions. (Level of evidence: Low; Strength of recommendation: Weak).

4.4. Targeted therapies

4.4.1. ACP

Approximately 70-95% of ACP patients have somatic mutations in the *CTNNB1* gene [18], but there are no specific targeted therapeutic agents for this mutation. The MAPK/ERK signaling pathway was found to be activated in β-catenin-dependent ACP tumor cells, and MEK inhibitors (e.g. temetoribine, bimetoribine) have shown some therapeutic efficacy in case reports [115]. For patients with elevated IL-6 concentrations in cystic fluids, the *anti*-IL-6 receptor monoclonal antibody tocilizumab may have therapeutic potential [116]. Currently, lacks of evidence of the effectiveness of PD-1/PD-L1 immune checkpoint inhibitors in pediatric craniopharyngiomas. All of these treatment options are in clinical trials.

Recommendation 35. Targeted therapies may be considered within clinical trials or with full informed consent after MDT discussion. for recurrent or refractory ACP. (Level of evidence: Low; Strength of recommendation: Weak)

4.4.2. PCP

Almost all patients with PCP have BRAF V600E mutations [18] and the results of relevant studies targeting BRAF and/or MEK inhibitors have been encouraging. A phase II clinical study confirmed the good therapeutic efficacy of vemurafenib in combination with cobimetinib [24]; another multicenter cohort study similarly showed significant efficacy of dabrafenib in combination with trametinib [117]. Currently, phase II clinical trials for the dabrafenib/trametinib combination regimen are still underway. In addition, a retrospective cohort study in adult Chinese patients also reported favorable responses and an acceptable safety profile with BRAF/MEK inhibitor therapy for BRAF V600E-mutant PCP [118].

For pediatric PCP, disease-specific prospective trials are not available because of its extreme rarity. However, pediatric PCP shares the core BRAF V600E driver alteration with adult PCP, and pediatric case reports and small series have described clinically meaningful responses to BRAF pathway inhibition. Therefore, in children with unresectable, recurrent, residual, or high-risk BRAF-mutant PCP, BRAF and/or MEK inhibitors may be considered after MDT discussion, preferably within a clinical trial or registry when available, or with full informed consent and careful monitoring of toxicity, tumor response, endocrine status, and long-term developmental outcomes. Given the limited pediatric evidence, routine debulking solely to enable targeted therapy should not be recommended; decisions should remain individualized and anchored in functional preservation [19,117,119].

For recurrent or refractory pediatric ACP, anti–IL-6 receptor (tocilizumab) and *anti*-VEGF (bevacizumab) therapy have shown benefit in case reports and may be considered in palliative or recurrent settings, pending further validation. Routine cytoreductive surgery prior to molecular targeted therapy is not currently recommended in children. For the rare pediatric PCP harboring BRAF V600E, BRAF/MEK inhibition may be offered by analogy to adult data after MDT discussion and informed consent.

Recommendation 36. BRAF/MEK inhibitors should be considered for BRAF-mutated PCP. (Level of evidence: Moderate; Recommendation strength: Strong)

4.5. Endocrine replacement therapy

The incidence and persistence of long-term endocrine dysfunction are higher when craniopharyngioma is diagnosed in childhood. Long-term treatment of adrenocorticotropic hormone, thyroid hormone and gonadotropin deficiencies in patients with craniopharyngiomas does not differ significantly from the treatment of pituitary deficiencies due to other causes. Hydrocortisone replacement therapy should be monitored clinically for signs of over- or under-exposure. Since patients with craniopharyngiomas are sometimes associated with malaise or hypothalamic obesity, which may be exacerbated by hydrocortisone, monitoring needs to be more careful. For thyrotropin deficiency, the goal of treatment is to bring free T4 (FT4) levels into the upper 1/3 to upper 1/2 range of the normal values. When combined with adrenocorticotropic hormone deficiency, glucocorticoid replacement therapy should be given before thyroid hormone replacement therapy. It should be noted that FT4 levels may decrease after replacement is started in the combined presence of growth hormone and/or gonadotropin defects, at which point the dose of levothyroxine sodium may need to be increased. Long-term hormone replacement therapy is essential, not only to improve quality of life, but also to reduce the risk of osteoporosis and significantly reduce cardiovascular risk [10]. Growth hormone therapy may be initiated in pediatric patients 6 months after completion of treatment for craniopharyngioma, provided that stability is confirmed by two consecutive MRIs 3 months apart [120]. In some children with severely affected growth and body mass index, growth hormone therapy may even be initiated as early as the 3rd month after completion of treatment. At present, there is no evidence that growth hormone therapy is associated with tumor recurrence.

The goal of endocrine replacement therapy is to mimic physiological hormone secretion as closely as possible, either by supplementing pituitary tropic hormones or their corresponding target gland hormones. In patients with multiple hormone deficiencies, adrenal glucocorticoids should be replenished first, followed by thyroid hormones, sex hormones, and GH. Hydrocortisone is the glucocorticoid of choice. For children, the total daily dose of hydrocortisone can be calculated based on 7–9 mg/m^2. Adequacy of daily replacement dose is assessed according to the patient's subjective symptoms and clinical indicators, including body weight, mental status, appetite, blood pressure, serum sodium, and blood glucose. Levothyroxine sodium (L-T4) is the recommended thyroid hormone replacement, with a usual daily dose ranging from 25 to 150 μg. Serum levels of FT3, FT4, TT3, and TT4 should be rechecked every 4–6 weeks, with the goal of maintain TT4 and FT4 within the normal reference range. For children and adolescents with growth hormone deficiency, the initial replacement dose is suggested to start at 22–35 μg/kg per day, adjusted based on body weight, growth velocity, or IGF-1 levels, with IGF-1 not exceeding the upper limit of the normal range for the respective gender and age. For girls without pubertal onset of central hypogonadism, replacement therapy—such as continuous sequential or cyclic sequential estrogen and progesterone therapy, GHRH pulsatile pump therapy, or combined HCG/HMG

treatment—should be managed under the guidance of pediatric endocrinologist or gynecologist. For boys without pubertal onset, replacement options include androgen replacement, GHRH pulsatile pump therapy, or combined HCG/HMG treatment, directed by a specialist in andrology or pediatric endocrinology. If a child has concurrent deficiencies in GH and the gonadal axis, GH supplementation should be initiated first. Sex hormone replacement therapy should be introduced gradually only after the child's height has reached near the normal range for age. This sequence helps maximize bone growth potential before puberty while avoiding the adverse effects of precocious puberty on final adult height.

Recommendation 37. Current evidence does not indicate that GH therapy increases the risk of craniopharyngioma recurrence. However, in the presence of active disease (radiologically evident progression), GH therapy should be withheld. Reinitiation may be considered after MDT discussion once the disease is stable (confirmed by two consecutive MRI scans showing no progression at 3- to 6-month intervals). (Level of evidence: High; Strength of recommendation: Strong)

Recommendation 38. In patients with gonadotropin-deficient pediatric craniopharyngiomas, it is recommended that puberty induction therapy be initiated at the age of physiological puberty, usually 11-13 years for girls and 12-14 years for boys. During induction, the development of secondary sexual characteristics, progression of bone age, and rate of height growth should be closely monitored, and psychosocial adjustment should be regularly assessed. Follow-up visits every 3-6 months are recommended. (Level of evidence: Moderate; Strength of recommendation: Strong)

4.6. Other complementary therapies

Management of hydrocephalus: Although the presence of hydrocephalus at the time of initial diagnosis is not necessarily an independent long-term adverse prognostic factor in itself [121], it must be aggressively managed for its etiology. However, the treatment of associated hydrocephalus should be targeted according to the condition. For acute intracranial hypertension, external ventricular drainage (EVD) should be performed as a matter of urgency to relieve symptoms, and the primary tumor should be actively treated. Ventricular changes should be closely monitored after tumor resection, and clinical symptoms and imaging changes should be regularly assessed during long-term follow-up. Multidisciplinary collaboration among neurosurgery, imaging and pediatrics is needed to dynamically assess the cerebrospinal fluid dynamics during management.

Recommendation 39. Acute intracranial pressure increase caused by hydrocephalus should be treated with emergency extraventricular drainage and active management of the primary tumor. Ventricular changes should be closely monitored after tumor resection. (Level of evidence: High; Strength of recommendation: Strong)

Vision preservation strategies: most children have visual impairment at the onset of the disease [122] and more than half have long-term visual impairment [123,124]. It is recommended that all children with craniopharyngioma complete a baseline vision assessment within 4 weeks of diagnosis. If visual acuity deficits are identified, testing should be repeated 4-6 weeks after the initial surgical intervention. Best corrected visual acuity (VA) must be used as a baseline at the time of evaluation. Follow-up visual acuity assessments may be performed every 3 months and can be synchronized with imaging assessments to provide a comprehensive assessment of treatment response. The frequency of subsequent assessments should be determined by the primary care team based on the patient's specific risks [125].

Preoperative comprehensive ophthalmological evaluation should be performed, including visual acuity examination, visual field examination and fundus examination, combined with MRI to assess the degree of compression of the optic pathway by the tumor. Intraoperative monitoring techniques such as neuronavigation should be used to maximally protect optic pathway structures, and glucocorticoids should be used to reduce optic nerve edema if necessary. Postoperative visual acuity changes need to be closely monitored, and hormonal shock therapy can be considered if acute visual loss occurs. For residual visual impairment, refractive correction and amblyopia training should be carried out promptly with regular follow-up. If progressive vision loss is detected, tumor recurrence or radiation optic neuropathy (in patients receiving radiotherapy) should be screened to ensure timely intervention.

Recommendation 40. It is recommended that all children with craniopharyngiomas complete a baseline vision assessment within 4 weeks of diagnosis. If visual deficits are identified, testing should be repeated 4-6 weeks after the initial surgical intervention. Comprehensive preoperative ophthalmic evaluation, intraoperative preservation of visual function, and regular postoperative monitoring of visual acuity changes are recommended. (Level of evidence: High; Strength of recommendation: Strong)

Cognitive interventions: the degree of cognitive impact of craniopharyngiomas on children varies from person to person, with hypothalamic involvement being a core predictor, requiring preoperative assessment, delicate surgical procedures and long-term rehabilitation to mitigate sequelae [126–128]. Cognitive functioning interventions should be based on a multi-stage, individualized and comprehensive management model. A cognitive baseline can be established before and after treatment with neuropsychological assessments such as the Wechsler Intelligence Scale for Children (WISC) [129]. Computer-assisted cognitive training (e.g. Cogmed Working Memory Training [130]) should be initiated in the early postoperative period in conjunction with behavioral therapy to improve attention deficits. In the mid-term (approximately 3-6 months), an individualized education plan is required to provide academic adjustment support. Neuropsychological review should also be conducted at regular intervals (e.g. every 6-12 months), focusing on executive function, memory and mood states, and the family-school-medical team needs to collaborate to provide structured environmental support and psychological interventions to minimize the cognitive sequelae of hypothalamic injury.

Recommendation 41. Preoperative assessment, meticulous surgical techniques, and long-term rehabilitation management to mitigate the impact of craniopharyngioma on children's cognitive function. (Level of evidence: High; Strength of recommendation: Strong)

Nutritional support**:** Nutritional management of children with craniopharyngioma requires staged and individualized interventions. In the acute postoperative period (1-7 days), the first priority is to maintain the stability of vital signs, focusing on the monitoring of blood sodium and other electrolyte levels, accurate recording of intake and output, and timely control of water-electrolyte balance [131–133].

In terms of nutritional support, a progressive, individualized feeding strategy is recommended in the early postoperative period. Overfeeding should be avoided, as high-calorie support is often not beneficial postoperatively. Swallowing function should be assessed first, and those who are at risk of aspiration should be temporarily fasted and given intravenous nutritional support; once swallowing is adequate, feeding may progress from clear liquids to a balanced, high-protein diet sufficient for postoperative recovery; caloric intake should be kept at recovery-appropriate levels rather than excessive, and a structured long-term calorie-controlled plan should be instituted thereafter to prevent hypothalamic obesity. Special attention should be paid to the possibility of delayed gastric emptying in the postoperative period, which requires close observation of symptoms such as abdominal distension and vomiting, and the administration of gastrointestinal stimulant drugs if necessary.

Long-term nutritional management focuses on the prevention and treatment of metabolic disorders resulting from hypothalamic injury.

Common problems include: (1) abnormal appetite regulation (bulimia or anorexia), which requires the establishment of a regular meal plan and control of the eating environment; (2) disorders of energy metabolism, which suggests controlling the intake of refined carbohydrates; and (3) abnormalities of body fat composition, which require regular monitoring of body fat percentage and lean body mass, and the development of an individualized exercise program. It is also important to pay attention to bone health, ensuring adequate calcium and vitamin D intake and regular monitoring of bone density. It is recommended that a comprehensive nutritional assessment be conducted every 3-6 months to adjust the intervention program in a timely manner in order to improve the long-term prognosis and quality of life of patients. Throughout the process, special attention should be paid to the nutritional education of patients and their families to help them establish a scientific concept of dietary management.

Recommendation 42. Staged, individualized nutritional management of children with craniopharyngioma. (Level of evidence: Moderate; Strength of recommendation: Strong)

Management of hypothalamic obesity: obesity and eating disorders in approximately 40-50% of children with craniopharyngioma[118]. Postoperative weight monitoring and intervention should begin as early as possible, and the risk of postoperative weight gain and hypothalamic obesity should be thoroughly communicated with the family before surgery to establish realistic expectations and ensure family support. The management of hypothalamic obesity in children after craniopharyngioma surgery requires a multimodal, integrated intervention strategy that focuses on abnormal appetite regulation and impaired energy metabolism due to hypothalamic damage. Measures such as the following may be effective in the treatment of hypothalamic obesity in children: melatonin replacement therapy: to improve circadian rhythm disorders and daytime sleepiness [134,135]. Central stimulants: modafinil (100-400 mg/day) or methylphenidate (10-30 mg/day): improvement in somnolence and body weight [136]. Dextroamphetamine: stabilizes BMI and improves mobility (requires gradual dose adjustment) [137,138]. Octreotide: short-term inhibition of β-cell activity, initial weight loss but accompanied by gastrointestinal side effects, long-term efficacy is not clear [139,140]. Emerging pharmacotherapies for hypothalamic obesity include setmelanotide (MC4R agonist) and GLP-1 receptor agonists (e.g., liraglutide, semaglutide). Both show promise in select refractory cases, though pediatric evidence remains limited. They may be considered under close monitoring and MDT guidance with informed consent.

Lifestyle intervention: appropriate increase in physical activity. Early systematic intervention can significantly improve prognosis, but lifelong follow-up management is required.

Recommendation 43. Management of hypothalamic obesity in children after craniopharyngioma surgery requires a multimodal, integrated intervention strategy that focuses on abnormal appetite regulation and impaired energy metabolism due to hypothalamic injury. (Level of evidence: Moderate; Strength of recommendation: Strong).

4.7. Multidisciplinary treatment strategies for complex cases

Multidisciplinary team (MDT) management is essential for all children with craniopharyngioma, not only complex cases. Even apparently straightforward cases benefit from coordinated endocrine, ophthalmologic, and neuropsychological oversight, because initial management decisions made without MDT input may compromise long-term tumor control and functional outcomes. The following section focuses on complex cases, where MDT coordination is most critical, but the same principle applies throughout. For complex cases of craniopharyngioma in children (e.g. large tumor, severe hypothalamic involvement, recurrence or with significant complications), multidisciplinary teamwork is the key to optimize treatment decision-making and improve prognosis. The MDT team consists of: specialists from the neurosurgery, pediatric oncology, endocrinology, radiation oncology, ophthalmology, nutrition, psychiatry, and rehabilitation, to ensure all-round management. The combined treatment decision-making process includes the following aspects: preoperative evaluation: MRI to clarify the relationship between the tumor and the hypothalamus and optic pathway, endocrine evaluation (pituitary function), ophthalmological examination (visual field) and neuropsychological testing. Individualized surgical plan: priority is given to neuroendoscopic or microsurgery, with intraoperative navigation techniques to protect key structures; if the risk of total resection is high (e.g. hypothalamic adhesions), partial resection + postoperative adjuvant therapy is chosen. Postoperative adjuvant therapy: for residual tumors, radiotherapy (e.g. proton therapy) or intracapsular therapy (bleomycin), depending on age and location; endocrine defects (e.g. diabetes insipidus, growth hormone deficiency) require immediate replacement.

Recommendation 44. It is recommended that all pediatric craniopharyngioma cases, especially complex cases (e.g., large tumors, severe hypothalamic involvement, recurrence, or with significant complications) should be managed throughout the process by a multidisciplinary team (MDT). The multidisciplinary team should include specialists in neurosurgery, pediatric oncology, endocrinology, radiation oncology, ophthalmology, neuroimaging, neuropathology, nutrition, psychology, and rehabilitation to ensure comprehensive, multi-stage and individualized treatment. (Level of evidence: High; Strength of recommendation: Strong)

[Rationale and description] : For a wide range of complex tumors, the MDT model has been shown to improve the quality of decision-making and patient prognosis. For craniopharyngiomas, a disease that involves multi-system and multi-stage management, MDT is particularly valuable. The level of evidence and strength of recommendation are the highest.

5. Handling of special cases

5.1. Treatment of cystic craniopharyngioma

Cystic craniopharyngiomas in children have unique clinicopathological features and their treatment strategies need to be individualized according to the characteristics of the lesion. The cystic fluid often contains characteristic cholesterol crystals and protein components [141,142]. Due to the space-occupying effect of the cyst, children often show symptoms such as visual impairment, endocrine disruption, or hydrocephalus, and are highly susceptible to recurrence after simple puncture.

For therapy, intracapsular injection therapy offers an important option for recurrent or high-risk surgical cases [143]. Bleomycin inhibits the proliferation of epithelial cells in the cystic wall and needs to be injected in divided doses after a precise image-guided puncture [143–145]. Interferon-alpha works through the immunomodulatory pathway and is suitable for some cases intolerance to bleomycin [146]. All of these treatments need to be carefully tailored to the indications, with special attention paid to avoiding leakage outside the cyst or even into the ventricles. Bleomycin carries notable toxicity—including nausea, vomiting, fever, and, when leakage beyond the cyst occurs, rare but serious neurotoxicity such as encephalopathy and leukoencephalopathy—which has led many centers to abandon it in favor of interferon-α or other modalities. Owing to this toxicity, intracystic therapy (bleomycin or interferon) is now mainly reserved for young patients with recurrent/residual cystic lesions who are not suitable for radiotherapy or repeat surgery, serving as a bridge to defer definitive treatment.

Surgical treatment strategies need to take into account the anatomical location and size of the cyst. The endoscopic transnasal approach is suitable for cysts that are confined to the sellar region, with the

advantages of minimal trauma and rapid recovery, whereas for large cysts or lesions with combined parenchymal components, craniotomy may be required to ensure safe resection [59,147]. In technical manoeuvres, special attention is paid to the protection of the hypothalamus, pituitary stalks and optic pathway structures [59]. In high-risk cases, staged treatment or intraoperative placement of the Ommaya capsule may be used for follow-up management.

Postoperative management focuses on the prevention of recurrence and functional protection. A standardized follow-up system needs to be established to detect changes in the condition through regular MRI monitoring and endocrine assessment. For patients with recurrence, salvage measures such as reoperation, intracapsular therapy or radiotherapy should be chosen according to the specific situation. Throughout the treatment process, close collaboration of a multidisciplinary team is required to effectively control the tumor and minimize treatment-related complications to ensure the best long-term prognosis for the child.

Recommendation 45. The treatment strategy needs to be individualized according to the characteristics of the lesion, and intracapsular drug injection, craniotomy, endonasal endoscopic approach, and pharmacological treatment may be considered. (Level of evidence: Moderate; Strength of recommendation: Strong)

5.2. Management of postoperative residual craniopharyngiomas

Postoperative imaging, which reveals the presence of tumor remnants, should be managed aggressively, and studies have shown that any residue of the cystic wall of ACP may lead to recurrence [148]. Supplementary radiotherapy should be given, as described in section 4.2. The management of postoperative residual tumor should be individualized. Not all residuals will progress, especially small, stable calcifications. However, for residuals with growth potential (e.g., solid components, enhancing cyst walls), adjuvant therapy (e.g., radiotherapy) should be considered.

5.3. Management of recurrent craniopharyngiomas

The choice of treatment after recurrence needs to be individualized, and participation in clinical trials is recommended for recurrent refractory cases. For limited recurrence, secondary surgery remains the preferred option, but the risk-benefit ratio should be carefully evaluated [59]. Advances in endoscopic techniques have expanded the indications for transnasal surgery, allowing minimally invasive treatment in selected cases [149]. Radiotherapy is an option depending on the cystic solidity, size, and other characteristics of the lesion [150,151]. The use of radiotherapy has been shown to be an effective way of treating the lesion.

Pharmacological treatments have shown promise in some cases, such as tocilizumab and bevacizumab for ACP [152] and BRAF/MEK inhibitors for PCP [153]. Intracapsular injections of bleomycin can be considered for cystic recurrences, but strict indications are needed [154,155].

Recommendation 46. Participation in clinical trials is recommended for relapsed refractory cases. (Level of evidence: Moderate; Strength of recommendation: Strong).

5.4. Strategies for management of hypothalamic invasion

Assessment of hypothalamic invasion in childhood craniopharyngiomas requires a combination of tests [122,156]. High-resolution MRI is the main method of assessing hypothalamic involvement, and the relationship between the tumor and important structures such as the anterior wall of the third ventricle and the funiculus can be clearly observed by sagittal T2-weighted images.

Protecting hypothalamic function is a crucial principle in the treatment process [4,27]. In cases of confirmed hypothalamic invasion or dense hypothalamic adherence, functional preservation may require leaving tumor tissue in key functional areas, and the residual tissue may be more than a very small amount. In such cases, the goal should be long-term hypothalamic, endocrine, neurocognitive, and quality-of-life preservation rather than radiographic gross total resection alone. Planned subtotal resection followed by close observation or appropriately timed radiotherapy should be considered after MDT discussion. Long-term multidisciplinary follow-up, including endocrine, metabolic, neuropsychological, visual, and quality-of-life assessment, is essential for early detection and management of hypothalamic sequelae.

For severe hypothalamic complications that have already occurred, systematic management measures are needed. The management of metabolic disorder syndromes focuses on controlling pathological hunger and obesity and requires a multi-pronged approach of dietary control, pharmacological treatment and behavioral interventions. Lifelong follow-up should be established for all patients, with regular assessment of metabolic markers, cognitive function and quality of life, and an individualized long-term management plan should be developed by a multidisciplinary team.

Recommendation 47. Based on the principle of protecting hypothalamic function, surgery, radiotherapy and drug therapy are selected according to the specific situation. Severe hypothalamic complications require systematic and individualized management measures. (Level of evidence: High; Strength of recommendation: Strong)

6. Follow-up and long-term management

Long-term follow-up management of craniopharyngioma in children requires the establishment of a systematic and individualized monitoring programme. Imaging follow-up is the key to early detection of tumor recurrence. MRI and CT examinations are recommended every 3-6 months in the first 2 years after surgery, focusing on changes in the saddle region and hypothalamus region and the presence of calcification. 6-12 months follow-up can be extended appropriately during the period of 2-5 years, and annual lifelong follow-up is still required after 5 years [125]. In children who have received radiotherapy, special attention should be paid to the monitoring of delayed radiation damage, including the possibility of cerebral white matter lesions and secondary tumors.

The frequency and content of follow-up should be individualized based on the patient's risk of recurrence. It is recommended to refer to the prognostic risk scoring model proposed in this guideline (see Table 5): For patients in the **low-risk group**, the standard follow-up schedule may be followed. For patients in the **moderate-risk group**, the imaging follow-up interval may be appropriately shortened (e.g., MRI every 3 months for the first 2 years), and endocrine and cognitive function assessments should be intensified. For patients in the **high-risk group**, in addition to the most rigorous imaging surveillance, more intensivemultidisciplinary team evaluations (e.g., every 2-3 months) should be conducted, and interventions for recurrence or functional deterioration should be planned proactively.

Endocrine function should be assessed throughout the child's growth and development [10]. Acute complications such as diabetes insipidus and adrenal insufficiency need to be closely monitored in the early postoperative period, and thyroid, adrenal, and gonadal axis functions need to be tested every 3 months. Special attention should be paid to sexual development after puberty, and children with growth hormone deficiency need regular assessment of IGF-1 levels and growth rate. All hormone replacement therapies need to be dynamically adjusted according to test results to maintain normal growth and development.

Assessment of neurocognitive function is critical to the child's learning and quality of life. Comprehensive neuropsychological testing, including core indicators of intelligence, memory and executive function, is recommended 1 year after surgery. In school-age children, the

focus should be on the development of academic skills and, if necessary, an individualized educational program should be developed. Children after radiotherapy are at higher risk of cognitive decline and require shorter assessment intervals of 6-12 months and enhanced cognitive rehabilitation.

Postoperative assessment of visual acuity, visual field and fundus should be performed, after which the frequency of follow-up visits should be adjusted according to the degree of stabilization of the disease [121]. Visual rehabilitation may be considered for children with visual field defects. Any new onset of visual loss requires vigilance for the possibility of tumor recurrence or radiation optic neuropathy.

The follow-up program requires close collaboration between a multidisciplinary team of neurosurgeons, endocrinologists, ophthalmologists and psychologists. At the same time, emphasis should be placed on educating the parents of the children so that they can master the necessary observation points and ensure that they can detect abnormalities and seek medical attention in a timely manner. Through standardized long-term management, the prognosis of children can be maximally improved, helping them to achieve better survival and development.

Recommendation 48. Postoperative follow-up should include: (1) imaging of the sellar and hypothalamic regions; (2) endocrine assessment throughout growth and development; (3) comprehensive neuropsychological testing (intelligence, memory, executive function) at 1 year; and (4) visual acuity, visual field, and fundus examination. All follow-up should be guided by a multidisciplinary team. (Level of evidence: High; Strength of recommendation: Strong)

7. Prognostic assessment

7.1. Prognostic factors

Importantly, in childhood-onset craniopharyngioma, long-term prognosis is determined less by tumor recurrence per se than by the burden of hypothalamic dysfunction—including hypothalamic obesity, neurocognitive and psychosocial impairment, and neuroendocrine deficits—which is the principal driver of reduced quality of life and increased late mortality, as shown in long-term German (KRANIOPHARYNGEOM) and St Jude proton-therapy cohorts. The prognosis of craniopharyngiomas in children is influenced by a number of factors, which can be classified into three main categories:

Clinical factors: these include the child's age, symptom presentation and duration, hypothalamo-pituitary functional status, tumor size, site of presence, and strength of adhesion to surrounding tissues. Studies have shown that a lower age of onset (especially <5 years) is recognized as an independent risk factor for recurrence [157–159]. In addition, large tumor diameters (e.g. ≥ 4 cm) are often indicative of a more aggressive tumor, often occupying multiple intracranial compartments and encroaching on surrounding vital structures, making total resection more difficult and the prognosis relatively poor [160–162]. Radical resection is also often difficult to achieve if the tumor invades the hypothalamus or has a multicompartmental structure, further suggesting a high degree of aggressiveness [28,163]. Preoperative manifestations such as hydrocephalus, elevated intracranial pressure or optic nerve compression may also increase the complexity of the procedure, thereby increasing the risk of recurrence [157]. Another key factor is the location of the tumor and its adhesion to surrounding tissues. The risk of recurrence is significantly increased when the tumor adheres to or infiltrates the hypothalamus, third ventricle or key neurovascular structures [51,164–166]. Although abnormalities in hypothalamic-pituitary function (e.g. total hypopituitarism) are often suggestive of hypothalamic involvement, the statistical correlation with recurrence has not been clearly established [167,168]. The prognostic impact of the length of time between symptom onset and diagnosis has been less well studied, and the available studies have not confirmed its direct prognostic significance.

Pathological factors: mainly include histological subtypes and molecular markers. Childhood patients tend to have ACP, which are often associated with mutations in β-catenin (CTNNB1) and activation of the Wnt pathway; in contrast, PCP are rare in children, but are more common in adults, with BRAF V600E mutations and sensitivity to the MAPK pathway [23]. CTNNB1 mutations are specific to ACP, while BRAF V600E mutations are specific to PCP. Papillary tumors are usually more structurally intact, with less invasion of surrounding tissues, have a relatively good prognosis and can be significantly treated with BRAF/-MEK inhibitors [153,169,170]. Ki-67 proliferation index is a commonly used biomarker, and its high expression (e.g. $\geq$10%) suggests active tumor proliferation, and can be used as a reference indicator of recurrence risk when assessed in conjunction with tumor size and extent of resection [171,172]. In addition, the presence of wet keratinised squamous cell clusters in the histology is thought to be associated with the risk of recurrence; the presence of foci of tumor calcification has also been reported in studies to be associated with an increased rate of recurrence [158,173,174]. The prognostic value of other markers such as p53 and VEGF lacks uniform conclusions [28]. While the prognostic value of Ki-67 remains debated in the literature, the consensus panel recommends its routine documentation as a biological baseline.

Treatment-related factors should be interpreted in a balanced manner. Although gross total resection may reduce the risk of radiographic recurrence in selected cases, this benefit must be weighed against the risk of hypothalamic, endocrine, visual, neurocognitive, and quality-of-life impairment. Evidence from large pediatric cohorts, including German craniopharyngioma studies, has shown that postoperative hypothalamic damage is a major determinant of long-term morbidity, hypothalamic obesity, reduced quality of life, and mortality [36,61,63,64,165]. Therefore, surgical series reporting high gross-total-resection rates should be interpreted cautiously if long-term endocrine, hypothalamic, neurocognitive, visual, and quality-of-life outcomes are not adequately reported. For tumors with clear hypothalamic involvement, maximal safe resection or planned subtotal resection followed by observation or radiotherapy may provide a more appropriate balance between tumor control and functional preservation. For patients with a large proportion of cystic lesions, intracapsular therapy (e.g., interferon, radioiodine oil, or Ommaya capsule injection) may control the disease to a certain extent, but its impact on long-term prognosis needs to be further investigated. For PCP patients carrying the BRAF V600E mutation, targeted therapies (BRAF/MEK inhibitors) have shown promising tumor shrinkage results and have become a promising emerging treatment strategy [175]. Notably, children with hypopituitarism can receive pituitary hormone replacement therapy, such as growth hormone, under strict monitoring, and it has not been shown to significantly increase the risk of relapse [176,177].

In conclusion, the recurrence and prognosis of childhood craniopharyngiomas are mainly determined by the biological characteristics of the tumor and the treatment modality. Clinically, low age (<5 years), large tumor size, hypothalamic involvement and increased intracranial pressure suggest a worse prognosis; pathologically, high Ki-67 expression and the presence of specific molecular variants (e.g., CTNNB1 and BRAF V600E) can suggest a different prognostic course. The most influential factor is the therapeutic strategy: individualized, function-preserving multimodal management is essential to balance tumor control with long-term hypothalamic, endocrine, visual, neurocognitive, and quality-of-life outcomes. Radical resection should not be pursued at the expense of irreversible hypothalamic morbidity.

Recommendation 49. High-risk features such as age of onset <5 years, tumor diameter ≥ 4 cm, hypothalamic invasion/tight adhesions, multicompartmental growth, or associated hydrocephalus/intracranial hypertension are recommended as core indicators for assessing the risk of recurrence and surgical complexity. (Level of evidence: Moderate; Strength of recommendation: Strong).

Recommendation 50. It is recommended that the Ki-67 proliferation index be routinely recorded in the pathology report and used in conjunction with tumor volume and extent of resection as a reference for recurrence risk assessment. (Level of evidence: Moderate; Strength of recommendation: Strong)

Recommendation 51. Routine postoperative assessment of whether total resection has been achieved is recommended, and the next step of treatment should be assigned as early as possible in cases of incomplete resection, in order to reduce the rate of tumor recurrence and to improve the patient's prognosis. (Level of evidence: High; Strength of recommendation: Strong)

Recommendation 52. If the cystic component of the tumor is predominant, intracapsular therapy (e.g., interferon) may be combined, but close monitoring for recurrence is required. (Level of evidence: Moderate, Strength of recommendation: Strong)

Recommendation 53. In children (<5 years of age) who are younger and whose tumor has not been completely resected, radiotherapy may be delayed until the tumor has progressed or until age >5 years if the residual lesion is stable, in order to reduce the risk of cognitive impairment (Level of Evidence: Moderate, Strength of recommendation: Strong).

7.2. Prognostic scoring system

There is currently no internationally accepted prognostic scoring or grading system for craniopharyngioma in children. In this guideline, we propose a preliminary prognostic risk-scoring framework that integrates clinical, pathological, and treatment-related factors (Table 4) to support structured risk discussion and follow-up planning, and suggests corresponding management strategies accordingly (see Table 5). This model should be regarded as an exploratory adjunct rather than a prescriptive treatment algorithm. It should not replace individualized decision-making by an experienced MDT, because patients with the same score may differ substantially in tumor anatomy, hypothalamic involvement, visual/endocrine status, prior treatment, radiotherapy suitability, family preference, and local treatment resources. Its clinical validity and generalizability require prospective multicenter validation.

Patients were risk stratified and managed based on cumulative scores. Higher scores have a worse prognosis and more aggressive treatment and follow-up strategies are recommended:

Low-risk group (total score 0-2): Patients in this group are usually older cases with smaller tumors that have been completely resected. The risk of recurrence is low, so routine postoperative follow-up surveillance can be performed and no additional radiotherapy is required. In the case of PCP with detectable BRAF mutations, consideration of targeted therapy (BRAF/MEK inhibitors) is also a suitable option.

Medium-risk group (total score 3-5): Patients in this group may have larger tumors or hypothalamic involvement, where resection may be incomplete and the risk of recurrence is Medium. In this group, intensive follow-up and regular imaging (e.g., MRI or CT) are recommended. In addition, depending on the patient's specific situation, postoperative adjuvant therapy, including radiotherapy or targeted therapy, may be considered. Radiotherapy should be used with great caution in younger children (especially those under 5 years of age), and its potential long-term effects and benefits must be fully evaluated. Radiotherapy should only be used as a last resort when other treatment options are not effective in controlling the disease.

High-risk group (total score ≥6): patients in this group are usually younger cases with larger tumors that have not been completely resected and may have a high Ki-67 proliferation index or have not yet received radiotherapy. The risk of recurrence is high and intensive combination therapy, including postoperative radiotherapy, chemotherapy and other multidisciplinary interventions, is recommended. When considering radiotherapy, especially in younger patients, it is important to evaluate critically and carefully to ensure that the benefits of radiotherapy clearly outweigh its possible side effects. In these patients, the frequency of follow-up should be increased, with particular attention to tumor recurrence, pituitary function and neurological changes. At the same time, treatment should be individualized and adjusted according to the patient's response and treatment tolerance.

Recommendation 54. A multifactorial clinical prognostic scoring model may be developed and prospectively validated to support recurrence-risk assessment and follow-up planning in pediatric craniopharyngioma. Such a model should be used only as an adjunct to MDT-based individualized decision-making, not as a standalone basis for treatment selection. (Level of Evidence: Moderate; Strength of recommendation: Strong)

Recommendation 55. Validation of the validity and applicability of this scoring model in a multicenter prospective cohort and exploration of the potential for individualized treatment guided by other molecular markers is encouraged. (Level of Evidence: Moderate; Strength of recommendation: Strong)

[Rationale and description]: Risk stratification is a trend in modern oncology. This recommendation advocates the establishment and validation of prognostic models, which is an important direction for the advancement of the field. The concept is based on existing prognostic factor studies, so the evidence level is “moderate”, but its clinical guidance is significant, and the strength of recommendation is “strong”.

External review panel roster

Xiangen Shi (Department of Neurosurgery, Sanbo Brain Hospital, Capital Medical University); Hongyang Zhao (Department of Neurosurgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology); Tao Hong (Department of Neurosurgery, Jiangxi Key Laboratory of Neurological Diseases, the First Affiliated Hospital, Jiangxi Medical College, Nanchang University); Yao Zhao (Department of Neurosurgery, Huashan Hospital, Shanghai Medical College, Fudan University); Chaoyun Zhang (Department of Endocrinology and Metabolism, Huashan Hospital, Fudan University); Qingfeng Wu (Institute of Genetics and Developmental Biology, Chinese Academy of Sciences, University of Chinese Academy of Sciences). Representatives of the Chinese Craniopharyngioma Patients’ Support Group: Xixia Liu and Jianping Chen.

CRediT authorship contribution statement

Zhixiong Lin: Conceptualization, Data curation, Funding acquisition, Project administration, Supervision, Writing – original draft, Writing – review & editing. **Jie Ma:** Conceptualization, Funding acquisition, Supervision, Writing – original draft, Writing – review & editing. **Yonggao Mou:** Conceptualization, Investigation, Resources, Software. **Songtao Qi:** Writing – original draft, Writing – review & editing. **Xuejun Yang:** Conceptualization, Writing – original draft, Writing – review & editing. **Jianguo Xu:** Conceptualization, Writing – original draft, Writing – review & editing. **Yi Lin:** Methodology, Project administration, Validation, Writing – original draft, Writing – review & editing. **Yi Liu:** Project administration, Validation, Writing – original draft, Writing – review & editing. **Chuan Zhao:** Validation, Writing – original draft, Writing – review & editing. **Wenhao An:** Writing – original draft. **Feng Wan:** Validation. **Songbai Gui:** Validation. **Gao Zeng:** Validation. **Ping Liang:** Validation. **Yiguang Chen:** Validation, Writing – original draft, Writing – review & editing. **Yang Zhao:** Validation, Writing – review & editing. **Mingwang Zhu:** Validation, Writing – review & editing. **Chunde Li:** Validation, Writing – review & editing. **Jian Gong:** Writing – original draft, Writing – review & editing. **Yongxin Wang:** Validation. **Yaming Wang:** Validation, Writing – review & editing. **Jie Zhao:** Writing – original draft, Writing – review & editing. **Yan Ju:** Validation.

Ye Song: Writing – original draft, Writing – review & editing. **Xiaosheng He:** Validation, Writing – review & editing. **Xingfu Wang:** Software, Validation. **Xiaofang Yan:** Validation, Writing – review & editing. **Xianxin Qiu:** Writing – original draft, Writing – review & editing. **Hao Li:** Validation. **Yang Wang:** Validation. **Rong Zhang:** Validation, Writing – review & editing. **Jie Gong:** Writing – original draft, Writing – review & editing. **Xueling Qi:** Validation, Writing – review & editing. **Ming Ge:** Writing – original draft. **Julei Wang:** Validation, Writing – review & editing. **Qingguo Li:** Writing – original draft, Writing – review & editing. **Jun Fan:** Validation, Writing – review & editing. **Xiaobing Jiang:** Validation, Writing – review & editing. **Shibin Sun:** Validation, Writing – review & editing. **Wenzhong Mei:** Validation, Writing – review & editing. **Zheming Fang:** Validation, Writing – review & editing. **Song Han:** Validation, Writing – review & editing. **Bo Zhang:** Writing – review & editing.

Disclaimer

This guideline is based on existing literature and expert opinion and is useful for clinical decision-making, but is not a substitute for individualized treatment in specific cases, let alone a legal basis.

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Appendix A. Supplementary data

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