Diagnosis and management of children and adult craniopharyngiomas: a French Endocrine Society/French Society for Paediatric Endocrinology and Diabetes Consensus Statement

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Abbreviations

ACP: Adamantinomatous craniopharyngioma

ACTH: Adrenocorticotropic hormone
ADI: Adipsic diabetes insipidus
AMH: Antimullerian hormone
APC: Adenomatous polyposis
ASL: Arterial spin labelling
AVP-D: Arginine vasopressin deficiency
BMD: Bone mineral density
BMI: Body mass index
CP: Craniopharyngioma
CSF: Cerebrospinal fluid
CT: Computerised tomography
CTV: Clinical target volume
DNA: Deoxyribonucleic acid
dPCR: Digital polymerase chain reaction
EGFR: Epidermal growth factor receptor
FAP: Familial adenomatous polyposis
FSH: Follicle stimulating hormone
FT4: Free thyroxine
GDG: Guideline Development Group
GLP1: Glucagon-like peptide-1 receptor
GH: Growth hormone
GTV: Gross target volume
HE: Hematoxylin-eosin
HES: Hematoxylin-eosin-safran
HOb: Hypothalamic obesity
HRT: Hormone replacement therapy
ICD: Interface control document
IH: Intracranial hypertension
IL6: Interleukin 6
IL6R: Interleukin 6 receptor
IMRT: Intensity-modulated conformal radiotherapy
IFN α: Interferon-α
IQ: Intellectual quotient
iSGLT2: Inhibitor sodium glucose transporter type 2
LH: Luteinizing hormone
MAFLD: Metabolic dysfunction-associated fatty liver disease
MAPK: Mitogen-activated protein kinase
MRI: Magnetic resonance imaging
OCT: Optical coherence tomography
PCP: Papillary craniopharyngioma
PDGF: Platelet-derived growth factor
PD1: Programmed cell death protein 1
PDL1: programmed death ligand 1
PT: Planning Target Volume
PTCOE: Pituitary Tumor Centre Of Excellence
PTV: Planning Target Volume
rhCG: Recombinant choriogonadotropin alfa
RNFL: Retinal nerve fiberlayer
SCN: Suprachiasmatic nuclei
SE: Spin echo
SIAD: Syndrome of inappropriate antidiuresis
SMR: Standardized mortality ratio
VEGFR: Vascular endothelial growth factor receptor
V3: Third ventricle
WHO: World health organization

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Abstract

Craniopharyngiomas are rare hypothalamic-pituitary tumors found in young children, adolescents and adults, and their multidisciplinary management required, calls for consistent practices for practicioners, patients and families. The French Endocrine Society and French Society for Pediatric Endocrinology & Diabetes enlisted and coordinated adult and paediatric endocrinologists, neurosurgeons, pathologists, radiotherapists as well as psychologists, dieticians and a patient association, to draft a reference document on this severe disease.
The management of craniopharyngiomas remains complex due to their aggressive nature, invasive behavior, and propensity for recurrence, requiring a sequential and measured therapeutic approach and follow-up in expert centers. Although patient survival rates are high, the consequences of both the tumor and its treatment can lead to serious comorbidities and impaired quality of life, particularly in those patients with lesional hypothalamic syndrome. Recent advances have allowed the two described tumor types - papillary and adamantinomatous - to be associated with distinct molecular signatures, specific pathophysiological mechanisms and *ipso facto,* distinct therapeutic approaches, including innovative medications for hyperphagia, that will continue to evolve. This consensus statement covers all stages in the management of patients with craniopharyngioma, from diagnosis to therapeutic strategies including the long-term follow-up.

INTRODUCTION

Craniopharyngiomas (CPs) are rare brain tumors developing from malformations of embryonic remnants along the original pathway of the craniopharyngeal duct. Despite belonging to the group of benign epithelial tumors, defined by the World Health Organization (WHO), CPs are highly problematic in the clinical field because of the hormonal and hypothalamic disorders that they cause. CP can be divided into two distinct subtypes, adamantinomatous CP (ACP) and papillary CP (PCP), which differ both in their histological features and genetic alterations they carry, the latter being the source of new avenues for therapy. Currently, the management of CP remains complex, due to their invasive behavior, and propensity to recur, requiring sequential, a measured therapeutic approach and follow-up in expert centers. Aside from the tumour itself, the occurrence of endocrine deficiencies and hypothalamic syndrome represent major issues. The most important of these is intractable weight gain leading to severe hypothalamic obesity. Invisible disabilities include, among others, cognitive impairment, issues with emotional control, and altered quality of life or even social discrimination. These constitute underestimated consequences that require significant attention and dedicated care. Even today, the prognosis for patients with CP is an important issue, as a 3-fold higher overall mortality rate has been reported in CP patients compared to the general population.
Having recognized these challenges, a Guideline Development Group (GDG) was formed to develop a consensus on diagnostic and management recommendations for children and adults with CP. The GDG made 71 recommendations that are intended to provide an evidence-based and eminence-based document for clinicians in several disciplines involved in the care of patients with CP, to optimize the management of these rare tumors, improve the quality of clinical care, and thus improve health outcomes.

METHODOLOGY

This consensus document has been drafted under the shared responsibilities of the French Endocrine Society and the French Society for Pediatric Endocrinology & Diabetes. Guideline co-chairs (T.C., R.R., P.B. and B.G-C) identified topics related to CP diagnosis and management to be addressed. Twelve leading experts in endocrinology or neurosurgery (G.R., P.C., S.E., A.V., P.R., H.D., E.J., C.C., B.G-C., T.C., A.B-P., F.A.) supervised 10 working groups encompassing epidemiology, diagnosis, histopathology and molecular features, biochemical and imaging procedures, therapeutic strategies, hypothalamic syndrome and pituitary deficiencies, disability care, long-term follow-up

including the transition from child and adolescent to young adult (see Fig1). Members of the group were selected by the co-chairs according to their expertise in the specific topic, based on their clinical involvement and expertise as well as their recognized standing in the field. The task of each group was to carry out a bibliographic update of the main PubMed-indexed articles published since 2000. Only English-language and full-text articles were selected for analysis. The aim was to provide a document that incorporates recent advances and answers practitioners' practical questions. A first meeting was held on October 14th, 2022 with all participants, followed by a total of 4 virtual meetings every two months. During these meetings, published data were discussed between group members, then graded based on principles for grading of evidence for guidelines. Consensus recommendations were graded as weak or strong based on the quality of the evidence (Box 1). Once approved by coordinators the main document was sent for review to an independent group of reviewers (the list is provided at the end of the main document) on July 31st, 2023 for their criticism, comments and suggestions. Their recommendations were detailed by each session chair during a final virtual meeting on September 29th, 2023. Consensus was deemed to be obtained only if ≥ 70% agreement was achieved. In the case of disputes or close votes, recommendations were reformulated then proposed again for voting and consensus. After this meeting, presentations summarizing the consensus recommendations, summaries and discussion were produced for official presentation on October 6th, 2023 at the French Endocrine Society congress in Marseille, France. In parallel, a draft manuscript was prepared by the lead authors (T.C., R.R., P.B., B.G-C.).

Box 1. Grading of evidence and recommendations

Based on principles for grading of evidence for guidelines [1,2] as well as on previously published consensus statements from the French Endocrine Society and French Society for Pediatric Endocrinology & Diabetes Consensus Statement

Evidence

- Very low quality: expert opinion supported by one or a few small uncontrolled studies.
- Low quality: supported by large series of small uncontrolled studies.
- Moderate quality: supported by one or a few large uncontrolled studies or meta-analyses.
- High quality: supported by controlled studies or large series of large uncontrolled studies with sufficiently long follow-up.

Recommendations

- Weak: based on very low quality or low quality evidence.
- Strong: based on moderate quality or high quality evidence.

BACKGROUND

Epidemiology

- *Craniopharyngioma is a rare disease that requires multidisciplinary management in a Pituitary Tumor Center of Excellence (PTCOE) (strong).*
- *There is no clear environmental risk factor identified to date (strong).*

The incidence of CP is 0.5 to 2.5 new cases per million inhabitants per year worldwide [3]. Recent studies of national registries showed a similar incidence in the USA, with 1.7 cases/million inhabitants [4] and in Europe (with respectively 1.7 and 1.86 cases/million inhabitants in Sweden and Denmark) [5,6]. Only Japan appears to have a higher incidence in children (3.8 cases/million children)[7].

The annual incidence is similar to that described in the 1980s, and does not appear to have increased significantly over the last twenty years [8]. However, there has been an improvement in the recording of this pathology in registries [9]. The estimated prevalence is nearly 1 case / 50,000 inhabitants [4]. The age distribution of CP is bimodal, with a first peak in incidence observed in children (between the ages of 5 and 10), and a second peak in adults (between the ages of 55 and 69) [4]. No significant difference was observed in incidence rates between men and women [4–6,10]**.** CP accounts for approximately 1-3% of all brain tumours [8] and up to 5-10% of brain tumours in children [11]. ACP represents the most widespread subtype, and its frequency follows the bimodal distribution described above, while PCP is found almost exclusively in adults between the ages of 40 and 55[3]**.**

Environmental risk factors

Although no environmental risk factors for the development of CP have been clearly identified, some studies have shown geographical variations in the incidence of these tumours (e.g. in Japan) [12]. Although there are no studies analysing the direct relationship between environment and CP incidence, numerous studies have assessed the impact of environment on the occurrence of benign brain tumors, particularly in children. Among them, the recent study by Chang *et al.* demonstrated a link between benign brain tumours and air pollution [13]. However, the term "CP" is not included in any of these publications (even though it is one of the search terms in the ICD table).

Mortality

Although CPs are defined as benign tumors, excess mortality is still observed in patients diagnosed with CP. The SMRs (*standardized mortality ratios)* reported vary from 2.2 to 12.2, with the highest figures seen in patients diagnosed after age 65[14]. Wijnen *et al.* described an improvement in SMR over time, being respectively 6.2 and 2.9 for patients diagnosed before or after 2010 [15]. CPs diagnosed in childhood are associated with higher excess mortality than those diagnosed in adulthood [5,16]. Five and 10 year survival has been estimated at 81-94% and 70-93%, respectively [5,17]. Pediatric series have reported survival rates of 83-96% at 5 years, 65-100% at 10 years, and 62% at 20 years, with an SMR ranging from 2.88 to 9.28 [18,19]. Post-operative mortality (within 30 to 90 days following neurosurgery) ranged from 1.6 to 13% [17,20,21].

Mortality risk factors

The majority of studies show higher mortality in cases with anterior and/or posterior pituitary involvement [5,14–16]. In older studies, high doses of hydrocortisone may have contributed to increased cardiovascular risk. Furthermore, somatotropic insufficiency was rarely substituted [22]. Patients with CP have a higher mortality risk than patients with pituitary insufficiency related to other causes [23]. This is probably related to local aggressiveness of the CP, the frequency of recurrence and hypothalamic involvement. Studies of GH-substituted patients have reported lower mortality rates, inversely proportional to IGF1 levels [24]. Most studies have reported no difference in mortality according to the surgical technique used, in either adults or children [14,17,20,25]. Conversely, some studies have found excess mortality in the case of radiotherapy [5] but these results are

controversial[14,15,17]. One study, including pediatric cases, reported excess mortality which correlated with the residual tumor volume post-surgery, the irradiated volume and the need for a ventricular shunt[26]. Excess mortality was observed in female patients in all studies, without a clear explanation[5,14–16].

Causes of death

Few studies have described the causes of mortality. The most frequently reported causes were cardiovascular (24 to 56%)[5,15,22,24] (especially stroke) or respiratory system[15]. Cardiovascular disease is a result of the metabolic profile of these patients, induced by pituitary hormone insufficiencies and hypothalamic damage [27]. In addition, deleterious consequences of radiotherapy on blood vessels have been reported[24]. Once again, women appear to be at a greater risk of cardiovascular disease than men [28]. It is therefore essential in patients with CP, whose risk of developing cardiovascular disease is 3 to 19 times greater than that of the general population[22], to manage cardiovascular risk factors.

Corticotropic insufficiency and hydrocortisone supplementation have been cited as factors that increase the risk of infection and death [15,29]. Some of these infectious events are likely the cause of corticotropic decompensation. However, infections in CP patients appear to be less frequent in the most recently published studies (30% before 2010 and 15% after 2010)[16]. In an adult population over 65 years of age, a mortality rate of around 40% was observed, with a negative role for arginine-vasopressin deficiency (AVP-D)[14], the new term for diabetes insipidus[30].

During childhood, causes of excess mortality include: tumor progression, treatment side-effects, hypothalamic syndrome and its consequences, endocrine deficiencies, epilepsy, cardiovascular disease, non-alcoholic steatohepatitis, occurrence of other tumors, severe infections, and stroke [18,19]. These factors are probably due to more aggressive tumours, responsible for more frequent hydrocephalus and pituitary damage, as well as a higher frequency of recurrence and hence multiple treatments[31].

CLINICAL PRESENTATION

Clinical manifestations in children

- *Symptoms related to intracranial hypertension, headaches and visual disturbances are the main symptoms of craniopharyngioma in children (strong).*
- *The association of stunted growth with weight gain in children should systematically suggest a hypothalamic-pituitary disorder, in particular craniopharyngioma (strong).*

The most frequent symptoms at diagnosis are headaches (43-77%), with a heterogeneous presentation [32–37]. Because of the delay in diagnosis, clinical manifestations in children reflect more advanced forms of intracranial hypertension (IH), and visual impairment, with consequent sequelae of varying severity[38]. Signs of hydrocephalus and/or IH, including headaches and vomiting, have not been noted in all cohorts and are present in 40-77% of cases[33,34,39]. The presence of visual disorders is highly variable, occurring in 36% to 83% of children [32,34–37], but these are usually more severe at diagnosis than in adults [40]. In a series of 172 patients, Gautier *et al.* reported visual acuity of less than 1/10 in 9% of adults, compared with 25% of all children and 42% of children ≤ 10 years old [40]. These visual disorders may also result in visual field defects due to compression or damage of the optic chiasm, or secondary to disorders associated with IH (diplopia due to damage of the oculomotor nerve VI). Neurological deficits or signs have been rarely reported in cohorts, probably because they are not commonly investigated at diagnosis and/or due to their heterogeneous reported prevalence (between 3% and 46%) [33–35,39]. Pituitary endocrine deficiencies are frequent at diagnosis, even if they are not systematically the mode of discovery. GH deficiency is one of the most frequent deficiencies, such that a slowed growth rate is present in nearly 30% of children [33–35,37]. A polyuria-polydipsia syndrome, revealing an arginine-vasopressin deficiency (AVP-D) (formerly termed central diabetes insipidus), may be present at diagnosis (2 to 15% of cases) [32,34,36–39]. Obesity or overweight is found in around one third of patients [34,37,39,41] but these are rarely the

signs that lead to the diagnosis. The association of stunted growth with weight gain should systematically suggest a hypothalamic-pituitary disorder, in particular CP. Lastly, it should be emphasized that cognitive disorders, with recent and/or unusual difficulties at school, may be indicative of CP in children[42]. The circumstances of diagnosis during adolescence are the same as those in childhood (growth delay, visual signs, IH), with the addition of delayed puberty [34,43].

Clinical manifestations in adults

- *Headaches, usually retro-orbital, visual disturbances and/or endocrine deficiencies are the main clinical signs of craniopharyngioma in adults (strong).*

The modes of discovery are variable, and may associate visual symptoms, endocrine disorders, signs of IH and focal neurological signs[38,44–47]. It is likely that CP are progressive tumors, therefore the time between first symptoms and diagnosis can vary widely from a few weeks to several years [38]. Headaches and visual disturbances are the two most frequent symptoms. Headaches (present in half of all adults with CP) are most often retro-orbital, sometimes involving the vertex, and slowly worsen. More rarely, these may become more intense, with the usual analgesics being ineffective, and associated with nausea and vomiting (present in around a quarter of adults), constituting signs of an established or developing IH. The latter is most often associated with large cystic forms of CP or obstructive hydrocephalus, generally due to compression of the third ventricle (V3) and obstruction of the foramen of Monro. IH can be life-threatening in the short and longer term or cause optic atrophy that may compromise visual prognosis. Both visual acuity and visual field are affected. Damage to the visual field is often asymmetrical and depends on the location of compression, where compression of an optic nerve will result in monocular amputation of the visual field, a chiasmatic mass effect will be responsible for bitemporal hemianopia, while compression of the optic bands will be responsible for homonymous lateral hemianopia. The more severe and long-standing the compression is, the more severe the visual impairment, and the more unpredictable is the recovery. Involvement of the other cranial nerve pairs is less common in adults. Hypothalamic neurological signs are more rarely in the foreground but can include drowsiness, psychomotor slowing, mood alteration, attention and concentration disorders, eating disorders with weight gain that may eventually lead to obesity, and anterograde memory disorders[47]. Cognitive dysfunction presenting as the initial symptom of a CP is likely the manifestation of an obstructive hydrocephalus[48]. Seizures, or even more severe neurological disorders such as hemiparesis, or balance disorders may also be observed in exceptional cases. Over 80% of CP patients have an endocrine deficit at the time of diagnosis [49]. In adults, hypogonadism is the most prominent feature, presenting as amenorrhea in women and sexual dysfunction in men. Polyuria-polydipsia syndrome, indicating AVP-D, is also a possible mode of discovery of the lesion (20% of cases) [38]. Finally, a small (but growing) proportion of CPs, ranging from 1% to 3%, are discovered as pituitary incidentalomas [50,51]. In the latter case, these tumors are characterized by the absence of endocrine deficiencies, normal patient height and body mass index, the absence of hydrocephalus and a smaller tumor volume at diagnosis, compared to CPs diagnosed on clinical symptoms.

INVESTIGATIONS AT DIAGNOSIS

Biochemical and hormonal analysis

- *In children and adults, endocrine and biochemical evaluations should include the following assays: cortisol and ACTH (8 am), TSH and fT4, FSH/LH and peripheral hormones (estradiol in women of childbearing age, total testosterone in men), IGF-1, prolactin and natremia (strong).*
- *Assessment of the gonadotropic axis should only be carried out from the pubertal period onwards (strong).*
- *Dynamic assessment of the corticotroph axis may be considered if cortisol levels are between 138 to 500 nmol/L* (strong).*

- *The existence of a polyuria-polydipsia syndrome associated with a hypothalamic-pituitary lesion suggestive of a craniopharyngioma is a contraindication for water deprivation test (strong).*

Hormonal investigations to be carried out in the presence of a lesion resembling craniopharyngioma are designed to assess the lesional impact of the tumor, prior to its therapeutic management. They include the assessment of:

- **Corticotroph axis** by measuring cortisol and corticotropin (ACTH) levels, ideally at 8 a.m. (but at any time of day if acute corticotropic deficiency is suspected). In this case, substitution should be started in emergency after sampling, without waiting for the hormonal results. In line with previous recommendations [52], the diagnosis of corticotropic insufficiency can be made when plasma cortisol level at 8 am is below 138 nmol/L, and can be excluded if cortisol level is above 500 nmol/L*. Dynamic assessment may be considered if the cortisol level is between 138 and 500 nmol/L.
- **Thyrotroph axis** by measuring free thyroxine (fT4) and thyroid-stimulating hormone (TSH).
- **Gonadotroph axis** by measuring pituitary gonadotropins (LH and FSH) and peripheral hormones (estradiol in women of childbearing age and total testosterone in men). Assessment of the gonadotropic axis should only be carried out from the pubertal period. Inhibin B may also be measured in male adolescents.
- **Somatotroph axis.** No dynamic test must be performed before surgery. Only a low preoperative IGF-1 value is indicative of GH deficiency. Exploration of this axis is most often carried out, mainly in the postoperative period, by dynamic testing given that IGF-1 is an insufficient marker for the diagnosis of GH insufficiency [53]. However, dynamic explorations are also less relevant in the context of obesity.
- **Hyperprolactinemia** can be observed by compression of the pituitary stem (disconnection hyperprolactinemia).

**Cortisol values may vary depending on the assay kit used.*

With the exception of corticotroph insufficiency, which requires urgent and systematic treatment (including the introduction of a perioperative substitution protocol if necessary) [52], the existence of a deficiency does not necessarily indicate preoperative substitution. Nonetheless, it does allow documentation of the functional consequences of the lesion prior to hypothalamic-pituitary surgery. In children, however, thyrotropin deficiency should be replaced as soon as it is diagnosed. In adults, preoperative replacement of a thyrotroph deficit depends on the estimated time of onset, depth, and clinical impact.

- **Arginine-vasopressin deficiency (AVP-D)** is suspected preoperatively in the presence of a polyuria-polydipsia syndrome, whether or not it is associated with hypernatremia. AVP assay is not recommended due to problems with the performance of assay kits. The existence of a polyuria-polydipsia syndrome associated with a hypothalamic-pituitary lesion likely suggestive of a CP is a contraindication for the potentially harmful water deprivation test. Note that polyuria may be masked in the case of corticotropic insufficiency.

Overall, at diagnosis, over 50% of children and 40% of adults have at least one pituitary deficiency (Table 1).

Imaging

- *Imaging of craniopharyngioma relies on pituitary MRI, possibly combined with a cerebral CT (computed tomography) scan (strong).*
- *The aim is to specify the diagnosis, determine the topography of the lesion and its relationship with the visual pathways, and assess the risk of adhesions to the hypothalamus as part of the pre-surgical work-up (strong).*

- *Visualization of the third ventricle (V3) and its proximity to the tumor is of the utmost importance before surgery (strong).*

Imaging in children and adults is performed using magnetic resonance imaging (MRI), according to the usual modalities. Whenever possible, 3 Tesla image acquisition is preferred. Cerebral CT can sometimes be performed (for assessing calcification) but is not mandatory. The examination protocol, which focuses on the sellar region, differs from conventional pituitary MRI. The recommended sequences are as follows:

- T1 spin echo (SE) with and without gadolinium injection in 3D, if the MRI permits it. Otherwise, thin sections (2 to 2.5 mm) in the sagittal and coronal planes are recommended.
- Coronal T2 thin sections (2 mm) centered on the pituitary gland and lesion.
- 3D T2 (such as FIESTA, CISS, HyperCUBE) centered on the lesion and the floor of the third ventricle (V3), or alternatively sagittal T2 acquisition.
- 3D-FLAIR.

Diffusion and perfusion imaging (ideally by arterial spin labelling – ASL-) may be of interest in differential diagnosis. Although there are no pathognomonic signs of CP, some aspects are highly suggestive, which make a preoperative biopsy sometimes required for etiological diagnosis. On the other hand, it can be discussed, when surgery is avoidable, for the purpose of identifying and clarifying a somatic genetic alteration that could indicate targeted therapies (see Molecular Biology). As differential diagnosis from other lesions observed in the same region is sometimes difficult (germ cell tumor, glial or glioneuronal tumor, hemangioblastoma, pituicytoma, Langerhans histiocytosis), it is worth including sequences that are useful for differential diagnosis in the initial workup (diffusion, perfusion, 3D FLAIR). MRI therefore seeks to identify the following different features.

Arguments in favor of a craniopharyngioma

- ACP are frequently voluminous, multiloculated or solid-cystic, predominantly cystic, with walls that are raised and contain calcifications [46]. They typically develop at the junction of the stem and pituitary gland, and often remain within the cisterns (Fig. 2).
- Papillary craniopharyngioma are usually tissue-based or uniloculated, non-calcified and develop more proximally, within the infundibulum or V3 (Fig. 3).

Several recent studies have shown interesting results for differentiating the two subtypes of CP, according to radiological [54] or radiomics criteria, without, however, providing a guarantee of precise differentiation[55,56]. Better pre-surgical discrimination of the two subtypes could, in time, change practices in view of the targeted therapies now available.

Indications of severity on imaging

Elements of severity are mainly represented by the hydrocephalus and potential damage (compression, edema) to visual pathways (optic nerves, chiasma, optic bands).

Aspects of the surgical procedure

The topography of the lesion is important in determining the surgical approach and the risk of adhesions to the hypothalamus. It should be assessed in the sagittal plane on 3D T2 acquisition (Fig. 4), but also in the coronal plane, by observing the position of the hypothalamus in relation to the tumor. Various classifications have been proposed, including Prieto's classification[57]. CP can be sellar-suprasellar, pseudo-V3 (within the cisterns pushing back the floor of the V3), secondary V3 (suprasellar and within the V3 crossing the floor), infundibulo-tuberian (centered on the infundibulum and hypothalamus), and strictly within the V3. The elements that separate these 5 topographies are:

- The floor of the V3, which is clearly at a distance from the lesion for suprasellar locations.
- Mamillary bodies to distinguish lesions originating in the cisterns from intraventricular lesions: a high position favors a lesion in the cisterns (pseudo-V3 or secondary V3). A low position favors an intra-V3 lesion (FIG.3) [58].

- Sagittal view of the pituitary stalk: an intact stalk below the lesion favors a purely intra-V3 lesion. Conversely, amputation of the proximal part of the stalk suggests infundibulo-tuberian localization.
- The position of the hypothalamus in the coronal section: the hypothalamus being in the upper third of the lesion suggests a lesion of the cisterns, either supra-sellar or pseudo-V3. The hypothalamus in the lower third of the lesion is in favor of a purely intra-V3 lesion. The hypothalamus in the middle third of the tumor is in favor of an infundibulo-tuberian or secondary intra-V3 localization, which are the two topographies most at risk of adhesion to the hypothalamus.
- Finally, attention should be paid to the lesion's relationship with nearby vascular structures and cranial nerves, such as the oculomotor nerves (III).

Visual explorations

- *A complete neuro-ophthalmological examination, including visual acuity, optical coherence tomography (OCT) and visual field, is recommended for any diagnosis of craniopharyngioma (strong)*

Impaired visual function(s), common in CP, may be the mode of discovery of the disease or can be discovered during diagnostic evaluation, particularly in the pediatric population where visual symptoms are rarely expressed subjectively. Exploration of the visual pathways is always necessary in the diagnostic work-up of patients with CP. All the following visual functions should be assessed where CP is confirmed:

- Visual acuity must be assessed with and without correction, monocularly on the right and left eye, respectively, and binocularly. Normal visual acuity does not guarantee normal visual function. In fact, a patient presenting with an altered visual field that spares the central visual zone may still have intact visual acuity. A decline in visual acuity is common. In the study by Karavitaki *et al.* [38] which included 121 patients, 39% of children and 40% of adults had decreased visual acuity at diagnosis. In the study by Chen *et al.* 36% of patients showed a reduction in visual acuity at diagnosis[59].
- Macular and optic nerve OCT (*Optical Coherence Tomography*) or RNFL (*Retinal Nerve Fiber Layer) is* an examination that objectively measures the various retinal layers, in particular the ganglion cell layer and optic nerve fibers. It is a rapid, reliable, and reproducible examination that has become indispensable for monitoring all neuro-ophthalmological pathologies. It is thought to have a predictive value in visual recovery after surgery[60]. OCT-A or OCT angiography can reveal alterations in perifoveolar and peripapillary vascular density[60].
- The 24-2 automated static visual field or the Goldman kinetic visual field can be used to identify visual field impairment and characterize the deficit. It should be noted that a reliable visual field measurement can be obtained as early as age 6. In all other cases, reliability indices exist to attest to a correctly performed examination. In most cases, the impairment will be quadranopsia or bitemporal hemianopia. The visual field is a subjective, patient-dependent examination that can be difficult to perform (children, asthenia, lack of concentration). In a series of 121 patients, 46% of children and 60% of adults had an altered visual field at diagnosis of the disease[38]. In the study by Chen *et al.*, 44% of patients had bitemporal hemianopsia [59].

The rest of the ophthalmological examination must be systematic. The fundus may reveal bilateral optic atrophy (52%) or, more rarely, papilledema (16%) [59].

HISTOLOGY, PATHOLOGY AND MOLECULAR BIOLOGY

- *Anti-beta-catenin immunostaining is recommended to confirm the adamantinomatous subtype of craniopharyngioma (nuclear staining) (strong)*
- *Given its focal distribution within the tumor, nuclear positivity for beta-catenin may be absent on very small samples of adamantinomatous craniopharyngioma (weak).*

- *The use of anti-BRAF V600E (clone VE1) immunostaining is not recommended for the diagnosis of papillary craniopharyngioma and should not be used as a surrogate for molecular biology testing (strong).*
- *Molecular analysis for somatic mutations in the CTNNB1 gene is not routinely recommended, as histological examination with immunophenotyping is usually sufficient for the diagnosis of ACP (strong).*
- *Molecular analysis for the BRAF p.V600E mutation is recommended for the diagnosis of papillary craniopharyngioma, and systematically recommended if treatment with BRAF/MEK inhibitors is considered (strong)*

The diagnosis of CP by histopathology is based on light microscopy of tumoral tissue fixed in buffered formalin and stained by Hematoxylin-Eosin-Saffron (HES) or Hematoxylin and Eosin (H&E). The 2021 WHO classification distinguishes two types of CP: adamantinomatous CP (ACP) and papillary CP (PCP)[61].

In nearly 95% of cases, PCP carries the V600E activating mutation of the *BRAF* gene (*B-Raf* proto-oncogene) [62]. The V600E alteration of *BRAF* is a somatic driver mutation accepted to be involved in the development of numerous tumor types, including melanoma, thyroid carcinoma and low-grade glioma in children[63]. This mutation has not been described at the constitutional level, and thus no association between the occurrence of PCP and any of the above-mentioned tumors has been described to date. This alteration induces constitutive activation of the MAPK (*Mitogen-Activated Protein Kinase*) signalling pathway. In ACP, a mutation has been identified in exon 3 of the *CTNNB1* gene in 70 to 95% of cases, depending on the sensitivity of the technique used [62,64]. The *CTNNB1* gene codes for beta-catenin, a cytoplasmic protein involved in intracellular signalling of the Wnt pathway. Apart from these driver mutations, craniopharyngioma, as a whole, have a relatively low non-synonymous mutation rate per megabase (0.9/Mb), similar to that found in a number of pediatric tumors, as well as in low-grade tumors in adults, such as WHO grade I meningioma [65,66]. In view of this, CPs therefore appear to be good candidates for targeted therapy, particularly in the case of PCP.

Histologically, the two types of CP are easily identified[67]. ACP is characterized by epithelial nests associated with aggregates of ghostly "wet" keratin [67]. These aggregates are highly suggestive of ACP and are not seen in PCP. The epithelium of ACP is typically bordered by a basal layer of palisading basophilic columnar cells covered by a network of star-shaped cells known as the "stellate reticulum". It also contains distinct rounded, “whorl”-like epithelial clusters. ACP frequently show chronic lymphocytic inflammatory infiltrates, fibrosis, areas of necrosis rich in cholesterol crystals, areas of macrophagic resorption with giant multinucleated cells and calcifications. ACPs may also show signs of ancient haemorrhage with deposition of hemosiderin pigment. The surrounding nervous tissue typically shows piloid gliosis, which should not be confused with pilocytic astrocytoma. The presence of these pronounced changes is unique to ACP and rarely observed in PCP. Although the characteristic appearance of ACPs makes positive diagnosis simple in most cases, anti-beta-catenin immunohistochemistry is recommended to confirm the diagnosis[64,68–70]. ACP is characterized by heterozygous activating mutations in the *CTNNB1* gene, encoding the beta-catenin protein. These mutations lead to nuclear translocation of beta-catenin in a restricted proportion of tumor cells. This nuclear translocation is detectable by immunohistochemistry and is mainly confined to the "whorl"-like clusters. Only nuclear immunopositivity is specific for ACP. Membranous immunostaining is non-specific. Because of its focal distribution within the tumor, nuclear positivity for beta-catenin may be absent in very small samples (biopsies). The morphology and biology of ACP recapitulates odontogenesis [71]. The presence in the sellar region of a tumour with odontogenic differentiation may be linked to the development of the adenohypophysis [72]. The latter is derived from Rathke's pouch, which forms by invagination of the roof of the *stomodeum*, the embryonic primitive mouth. ACP thus derives from remnants of Rathke's pouch, which therefore retains an "oral" differentiation program.

PCPs are characterized by a "budding" architecture with the formation of large, coarse, often agglomerated papillae[67]. These papillae present a fibro-vascular core covered by "standard" non-

keratinizing conventional squamous epithelium, with no atypia. There is no "stellate reticulum" or clusters of "wet" keratin. PCPs are generally devoid of the complex inflammatory changes seen in ACP. Molecular analysis to look for V600E mutation of *BRAF* is recommended to confirm the diagnosis, and recommended to be performed systematically if treatment with BRAF and MEK inhibitors are envisaged. The use of anti-BRAF V600E immunostaining (clone VE1) is not recommended for positive diagnosis and must be avoided for theranostic purposes. In PCPs, beta-catenin labelling is membranous while nuclear positivity is always absent. Compared with ACPs, the origin of PCPs is less clear. An origin from squamous metaplastic cells (cell clusters of the *pars tuberalis* of the adenohypophysis or epithelial lining of a Rathke's pouch cyst) has been suggested[73,74].

Nevertheless, if the CP presents i) a non-specific morphology on histology, possibly due to a small specimen (biopsy); ii) an ACP morphology without nuclear beta-catenin positivity; or iii) a PCP morphology without *BRAF* V600E mutation, it is necessary to look for mutations in *BRAF* (V600E) and *CTNNB1* (exon 3) and, if negative to look for mutations in the adenomatous polyposis coli (*APC)* gene (**Fig 5**). Molecular techniques must be adapted to the specific mutation, be as sensitive as possible, and be at acceptable cost. Current practice favors techniques that allow detection of low-frequency mutations, such as high-throughput sequencing or, for identifying V600E *BRAF* mutations, digital polymerase chain reaction (dPCR). The presence of a *BRAF* V600E mutation points to PCP. The presence of a *CTNNB1* mutation (and exceptionally of *APC* mutation[75]) points to ACP. If the molecular work-up is negative, the histological diagnosis of CP should be reconsidered, and the case reviewed by an expert center. It is then recommended to determine the methylation profile of the tumor on formalin-fixed, paraffin-embedded material[69]. For example, a score above 0.9 in the Heildelberg classifier (https://molecularneuropathology.org) for the methylation class "Adamantinomatous CP" or "Papillary CP" supports the diagnoses of ACP and PCP, respectively. Negative molecular results must always be considered in the light of the percentage of tumour cells. Indeed, a small, paucicellular sample gives a risk of false negatives.

As previously mentioned, almost all CPs are sporadic tumors caused by somatic mutations known as "driver" mutations, with no hereditary genetic predisposition. In familial adenomatous polyposis (FAP), an inherited autosomal dominant disease, the Wnt pathway is activated following biallelic inactivation of the *APC* gene, a negative regulator of this pathway. This results in nuclear translocation of beta-catenin in the absence of *CTNNB1* mutation. Although the tumorigenesis pathway is identical, ACP is not a lesion classically associated with FAP. Only a few observations describing the occurrence of ACP in patients with FAP have been reported [76–80]. Interestingly, loss of the second *APC* allele at the somatic level has been observed in 3 out of 4 patients with an *APC* germline mutation, which is in favor of the involvement of APC in the CP found in these patients [81,82]. Moreover, a case of ACP associated with somatic biallelic inactivation of the *APC* gene, but without mutation of the *CTNNB1* gene, has been described in the literature[75]. In 6/9 patients with FAP and ACP, there is an ectopic, cerebellopontine localization of the CP. Consequently, in the presence of an ACP without somatic *CTNNB1* mutation and with at least one of the following conditions: ectopic localization, personal or family history of CP, or tumors in the FAP spectrum (colon cancer, osteomas, epidermoid cysts, desmoid tumors), or somatic *APC* mutation, looking for a germline *APC* mutation should be considered.

THERAPEUTIC MANAGEMENT

Box 2. General recommendations for the treatment of craniopharyngiomas

- *Any lesion found to be compatible with a craniopharyngioma should be referred to a Pituitary Tumor Centre of Excellence (PTCOE) (strong).*
- *In the case of preoperative hypothalamic syndrome, a conservative approach, as far as possible, is recommended since any dissection at the limits of the tumor entails a very high risk of aggravation (strong).*
- *In children and adults, the endonasal approach is recommended as the first-line approach for resection of craniopharyngiomas with median, suprasellar and retrochiasmatic extension (strong).*

- *In children and adults, the use of transcranial approaches for the resection of craniopharyngioma with non-cystic lateral extension in relation to the carotid axis is recommended (weak).*
- *Alternative medical treatments (targeted therapies) and/or radiotherapy, after tumor biopsy, should be discussed in cases of craniopharyngioma involving the hypothalamus in the absence of visual dysfunction (strong).*

Surgery

Approaches in children with craniopharyngiomas

- *In the case of intracranial hypertension due to obstructive hydrocephalus associated with a craniopharyngioma, ventriculoperitoneal shunting or cyst treatment (endoscopic emptying or placement of an Omaya drain) is recommended (strong).*
- *In the case of symptomatic optic tract compression, priority should be given to treatment of hydrocephalus and/or surgical decompression of the chiasma via a pterional trans-sylvian approach or endoscopic cystostomy (strong).*
- *Intrasellar craniopharyngioma that does not extend beyond the diaphragm should be treated endonasally by endoscopy or microscopy. Alternatively, treatment may be withheld under periodic radio-clinical supervision (weak).*
- *In children, suprasellar craniopharyngiomas require limited surgery to simply decompress the visual pathways and marsupialize the cysts, without attempting to pull towards the cisterns or cleave the ventricular wall, using an endoscopic trans-ventricular or trans-sylvian approach (weak).*

The surgical management of CP in children has evolved considerably since the early 2000's. Awareness of the possible adverse effects of surgery on academic performance, personality development, eating disorders and morbid obesity have been highlighted in various pediatric series [83,84]. Hypothalamic syndrome has been identified as being responsible for these complications, with greater impact seen in the growing child than in the adult who has already acquired a certain level of sociability, academic achievement and growth. This observation prompted neurosurgeons to move away from radiological classifications of CPs based on their relationship to the visual pathways, and to implement surgical strategies based on pre-operative radiological involvement of the hypothalamus [85,86]. The three-grade radiological classification of hypothalamic involvement proposed by Puget *et al.*, in particular hypothalamic involvement [87], was intended to assess the risk of developing hypothalamic syndrome postoperatively[83]. It was concluded that complete resection should be performed for grades 0 and 1, and only incomplete resection for grade 2, preserving the hypothalamus as much as possible. However, this classification has its limits, with the rate of hypothalamic syndrome remaining high postoperatively, including in grade 1. This suggests that the surgical procedure, and in particular traction manoeuvres on the ACP, known to be adhesive and invasive, should not be underestimated, and are likely responsible for these poor results. Very limited and cautious surgery; to open cysts and decompress visual pathways without traction on the tumour, is probably the most appropriate procedure, if followed by radiotherapy, without compromising prognosis [83,88–91]. This can be achieved via an endoscopic trans-ventricular or trans-sylvian approach, by simply opening the cystic lesions and resecting the portion compressing the visual pathways, without attempting to resect any part of the tumor that is close to the floor and without any traction. It is important to take into account, in this decision, the efficacy of radiotherapy, which has been accepted since the publication of Kramer et al. in 1960. Overall survival and progression-free survival did not differ between children who underwent large or moderate incomplete resection [88,92,93]. In conclusion, the optimal approach is most often towards the midline, either by endoscopic trans-nasal or ventricular endoscopy or the inter-hemispheric approach. Complete excision of suprasellar lesions is no longer recommended (see the surgery section).

Approaches in adults with craniopharyngioma

Five main categories of approach for resection of craniopharyngiomas are described (**Fig 6**):

- Standard endonasal transsphenoidal approach [94,95].
- Extended endonasal transsphenoidal approach, known as "transsphenoidal-transtubercular" approach.
- Supratentorial or infratentorial transcranial approach adapted to the exact location of the craniopharyngioma, usually derived from the pterional approach.
- Transventricular transcranial approach (transcortical - transfrontal or interhemispheric - transcallosal).
- Decompression procedures - cyst drainage - CSF bypass: ventriculoperitoneal bypass, intracystic drain placement, cysto-ventriculostomy.

Identifying the relationship of the craniopharyngioma to the sellar diaphragm, optic chiasm, pituitary stalk, and floor of V3 is the first major step in determining the choice of approach.

- ***Endonasal approaches***

- *In adults, for intrasellar or suprasellar craniopharyngiomas without supradiaphragmatic extension, the simple "standard" transsphenoidal approach is recommended (weak).*
- *In adults, for craniopharyngiomas with suprasellar transdiaphragmatic extension, and supradiaphragmatic craniopharyngiomas without lateral extension, the "extended" transsphenoidal approach through the tuberculum sellae turcica is recommended (weak).*

The extended endoscopic approach with resection of the tuberculum sellae and the sulcus opticus offers direct access to the supra-diaphragmatic, sub- and retro-chiasmatic spaces [96–100]. When CPs are located in this space, this approach allows resection without crossing the optic tracts with good control of the floor of the V3, optimizing preservation of these highly functional anatomical structures. The extended approach is associated with a high rate of radical resection and a limited rate of vascular and neurological complications [101–109]. In referral teams specialized in the management of these tumors, 80% of adult CP are operated on using the extended transsphenoidal approach. Cases of "transventricular" CP, also known as trans-infundibular CP, which have perforated the floor of the V3, may also benefit from resection using a "trans-tumoral" approach, i.e. following the corridor provided by the tumor resection [109]. This corridor provides access to the intraventricular portion of the CP, enabling resection via an extended transsphenoidal approach of extensive CP in the V3 via invasion of the pituitary stem and/or infundibulum, or direct perforation of the hypothalamic floor. These procedures are associated with a high proportion of subtotal resections, with no increase in hypothalamic risk, since penetration of the V3 follows the perforation created by the tumor [99,103,109,110].

- ***Closure step for extended transsphenoidal approach***

The closure step after extensive endonasal resection of CP must be performed with the utmost rigor. CSF leakage is inherent to endoscopic endonasal surgery when the supra-diaphragmatic space is approached. Intraoperative leakage is systematically observed. The closure stage is complex, as it involves managing a high-flow leak. If an extended transsphenoidal approach is required, we recommend specific prior treatment of hydrocephalus (most often by ventricular bypass), which, if left untreated, will constitute an obstacle to achieving tightness. A "multi-layer" skull base closure strategy is required. Reconstruction of the sellar floor with fascial plasty (fascia lata or synthetic) combined with vascularized nasoseptal mucosal flaps maintained with a transient Foley catheter has proven effective[111–114] as well as intra-extrasellar "champagne cork" fat plasty combined with fat packing of the sphenoidal sinus[115]. External lumbar drainage, associated with a significant risk of specific complications [116,117], is now less frequently used, as it carries its own morbidity in addition to that associated with CP resection. It is therefore not recommended.

Craniotomy approach (subfrontal, frontopterional, frontolateral, interhemispheric)

- *In children and adults, the use of a transcranial approach is also recommended for the resection of craniopharyngioma developed strictly in the V3, not extending to the pituitary stem, located above the hypothalamic floor without perforating it (weak).*
- *An intraventricular approach through a healthy V3 floor will inevitably result in postoperative hypothalamic syndrome and is not recommended (strong).*

The transsphenoidal endoscopic approach does not allow optimal control of tumour extension lateral to the axis of the supra-cavernous carotid arteries. Moreover, this approach exposes the surgeon to an increased risk of vascular complications through injury to the supra-clinoid carotid artery or one of its branches. Thus, apart from purely cystic lateral extensions, which can sometimes be resected by pulling on invaginations in the tissue using microtractions, suprasellar CPs with non-cystic lateral extension must be resected using a transcranial approach [94,118]. The exact location of the CP is not the only factor influencing the decision. The morphology of the sphenoidal sinus and the shape of the skull base, which must be opened to gain access to the tumor, must also be taken into account [119]. Apart from a perforation of the floor of V3, identifiable on MRI, an intraventricular approach through a healthy floor of the V3 runs a major risk of postoperative hypothalamic syndrome [120] and is not recommended. Thus, the rare cases of CP that develop strictly in the V3 must be operated via a superior transcranial approach (transcallosal or transcortical transventricular approach, or terminal lamina approach), although the risk of postoperative complications may be higher [94,120]. Thus, in cases of CP that involve the hypothalamus with no perforation through the floor of the third ventricle, the possibility of an alternative treatment to surgery (e.g., targeted radiotherapy or therapies) should be discussed.

- ***How to proceed to tumor resection?***

In practical terms, the strategy is to "stay within the tumor", without overstepping its boundaries, highlighting the concept of “trans-tumoral resection”. As CPs can lead to hypothalamic syndrome when they invade the floor of V3 [121,122], surgery, when it results in damage to the floor of the V3, can induce post-operative hypothalamic syndrome with dramatic neurological and psychiatric consequences. In the event of infiltration of the hypothalamus, subtotal resection should be preferred, leaving one or more remnants in contact with the hypothalamus. The literature has amply demonstrated the need for pituitary surgery to be performed by experienced neurosurgeons [123–126]. Given the relatively low incidence of CPs, the additional technical difficulty and the risk of damaging highly functional eloquent areas with serious consequences (hypothalamic syndrome), recourse to expert neurosurgical centers is necessary [127]. It should be emphasized that resection of CPs often requires dissection of the pituitary stalk, tumor excision within the invaded pituitary stalk, or even the sacrifice of the pituitary stalk. Moreover, anatomical respect for the pituitary stem does not guarantee preservation of pituitary function.The rise of endoscopic endonasal surgery [128], advances in radiotherapy in all its forms, a better understanding of the natural history of these tumors, and the neurosurgical community's awareness of the crucial need for hypothalamic sparing through pediatric studies, have all contributed to reducing current operative mortality to less than 5%[22].

Imaging in the immediate postoperative period

A post-operative check-up can be performed by MRI on day 0 or 1 with the following protocol:

- 3D T1 spin echo (SE) without and with gadolinium injection, or sagittal and coronal.
- 3D T2 or, failing that, coronal T2 thin sections (2 mm) centered on the pituitary gland and lesion.
- 3D FLAIR.
- Diffusion.

This imaging is used to check for possible complications, to assess visual pathways and the presence of tumor remnants. It should therefore only be proposed when necessary, by the medico-surgical team caring for the patient in the immediate post-operative period, based on clinical findings.

Depending on the topography, and in view of the functional risks associated with adhesion to the hypothalamus, a remnant in the hypothalamic region may be the expected post-operative outcome.

Radiotherapy

Normofractionated conformal radiotherapy (with recommended intensity modulation using photons or proton beams) is the gold standard for the treatment of CP in children and adults. However, until recently, recommendations for radiotherapy management have been hampered by the low level of evidence in published studies. Recent studies involving a large number of adults [129] and children [130] provide a new data base.
The literature on the use of radiosurgery and stereotactic radiotherapy in single-dose or hypofractionation is less robust than that reporting normofractionated conformal radiotherapy, due both to the scarcity of studies and to less-documented follow-up. This type of radiotherapy is aimed at smaller lesions, and at a distance from critical structures.

Indications for radiotherapy in the absence of prior irradiation

- ***Normofractionated conformal radiotherapy***

- *Combination of subtotal resection of the craniopharyngioma followed by complementary normofractionated radiotherapy can achieve similar local control, while reducing the surgical morbidity of maximalist surgery (strong).*
- *Normofractionated conformal radiotherapy may be proposed in cases of recurrence of craniopharyngioma, in the absence of previous radiotherapy (strong).*
- *Systematic postoperative radiotherapy is not indicated after complete gross total resection (strong).*
- *Proton therapy is an effective radiotherapy irradiation technique for the treatment of craniopharyngioma, optimizing the protection of healthy tissue compared with photons. It is proposed as an alternative to photon radiotherapy in pediatrics (weak).*

The consensus in the literature is that conservative surgery (subtotal or debulking/biopsy), combined, if necessary, with cyst emptying followed by complementary normofractionated radiotherapy should be the first line of treatment, resulting in improved local control (as opposed to exclusive surgery) and reduced surgical morbidity (as opposed to maximalist surgery)[88,131,132]. Radiotherapy may be deferred in certain cases, with close MRI monitoring, such as for patients of very young age (< 5 years) and/or slow tumor kinetics. In that situation, radiotherapy would be proposed at the time of re-evolution [133]**.** In terms of efficacy, the risk of recurrence is comparable between patients (adults or children) who have undergone extensive surgery or those who have undergone partial surgery followed by radiotherapy [134,135]. The combination of partial surgery and post-operative radiotherapy ensures a median progression-free survival of 60 months[88]. In another systematic review, 5-year PFS for patients treated with partial surgery and post-operative radiotherapy was 73%, and this rate did not differ statistically from that observed in patients with gross total resection[135]. Post-operative radiotherapy is not recommended after macroscopically complete surgery[136]. Although three-dimensional conformal photon therapy has been widely used, the most widely used technique currently is intensity-modulated conformal radiotherapy (IMRT). Proton therapy may be proposed for its ballistic advantages, but there is no formal evidence that it reduces the incidence of side effects, compared currently with IMRT. In a recent study, proton therapy prevented local recurrence in 92% of irradiated adult patients [129]. The use of proton beams in children is a priority for proton therapy departments in Europe and North America. Indeed, for this benign midline tumor, the dose to the target volume is similar to that delivered by photons, the dose upstream of the target volume is reduced, and with a complete absence of exposure of healthy tissue downstream of the target volume. The dose gradient between target and healthy tissue is thus greatly optimized. Savings are therefore mainly achieved in the brain parenchyma. A prospective study by Merchant *et al.* showed an improvement in cognitive outcomes after proton therapy, compared with photon therapy, in a cohort of 94 patients with a median age of approximately 9 years [130].

- ***Single-dose or hypofractionated stereotactic radiotherapy***

- *Stereotactic radiotherapy is not a first-line radiotherapy modality for the treatment of craniopharyngioma. Its indication should be discussed in a case-by-case basis by a dedicated tumor board (weak).*

When considering single-dose stereotactic radiotherapy (radiosurgery) or hypofractionated radiotherapy for 1st-line management of adult CP, data in the literature report tumor control rates lower than those reported with normofractionated stereotactic radiotherapy (control rate of 70% over a median follow-up of 45 months) [132,137]. Given the limited data available to date, this technique cannot be recommended.

Radiotherapy application

- ***Normofractionated conformal radiotherapy***

- *Gross Target Volume and Clinical Target Volume contours must be discussed in cooperation with the neurosurgical team (strong).*
- *In the case of a cystic component, several control images (CT or MRI) are required during radiotherapy to be able to adapt the target volume and dosimetry contours as the cystic component grows (strong).*

The target volumes reported for this type of radiotherapy are:
- *Gross Target Volume* (GTV, macroscopic volume taking up contrast medium on dosimetric MRI) including all three components: solid, cystic and calcified.
- *Clinical Target Volume* (CTV) (3D expansion of 5mm modified at uninvaded anatomical barriers [131,138]). The CTV is justified by the infiltrative nature of CP [139].
- *Planning Target Volume* (PTV) (3D expansion, the value of which is left to the discretion of each center depending on the particle, technique, restraint method and imaging control procedure employed - typically 3-7 mm).

GTV and CTV contours must be reviewed with the neurosurgical team. Doses delivered to the PTV range from 50.4 to 54 Gy with conventional fractionation [131]. In the case of CP with a cystic component, it is recommended to perform several follow-up images (CT or MRI) during radiotherapy, in order to propose adjustments to target volume contours and dosimetry in the event of cyst growth [140]. The organs at risk that must be delineated are the chiasma, optic nerves, brainstem, hippocampi, temporal lobes and cochleae [141]. Dose constraints are those reported in the literature by Lambrecht *et al.* [142] and by Noël and Antoni [143]. A mean dose ≤ 30 Gy to the left hippocampus is suggested to reduce cognitive impairment [144].

- ***Single-dose or hypofractionated stereotactic radiotherapy***

- *The target volumes to be reported for single-dose or hypofractionated stereotactic radiotherapy are the GTV and PTV. GTV contours should be discussed in cooperation with the neurosurgical team (strong).*

The unique target volume is:
- GTV (macroscopic volume taking up contrast on dosimetric MRI).
- The CTV is equal to the GTV.
- PTV (3D expansion, the value of which is left to the discretion of each center depending on the technique, restraint method and imaging control procedure employed - typically 0-3 mm).

Doses delivered to the PTV are 12-15 Gy as a single dose [145] and 18-21 Gy in 3 fractions or 25 Gy in 5 fractions.
The essential organs at risk to be delineated are the optic pathways and the brain stem [141]. Dose constraints are those reported in the literature by Milano *et al.*[146] and by Noël and Antoni [143].

Re-irradiation

In the event of re-irradiation, it is necessary to consider the doses previously received by organs at risk, particularly the visual pathways. The choice of radiotherapy technique should be discussed on a case-by-case basis during the tumor board review.

Targeted therapies

- *If standard treatment fails, targeted therapies (MEK or VEGF inhibitors, biotherapies) for adamantinomatous craniopharyngiomas should be discussed by a dedicated tumor multidisciplinary board (weak).*
- *For papillary craniopharyngiomas, combination of BRAF/MEK inhibiting therapies is a therapeutic option to be discussed by a dedicated tumor board (strong).*

Knowledge of the molecular biology underlying CP tumorigenesis has paved the way for an unsuspected field of application in these tumors. Somatic mutations of the *CTNNB1* gene are found in 70-95% of ACP[65]. These mutations lead to hyperactivation of the WNT pathway and also of the MAPK/ERK pathway, particularly at the invasive margins of the tumor [46]. There is also hypersecretion of growth factors (EGFR, PDGF, VEGF/VEGFR) and cytokines (IL6/IL6R, notably in the solid tumor component, but also in the cystic component), which contributes to tumor development. Hyperactivation of the PD1/PDL1 immune system has also been described [147] with two subtypes described: immunoresistant and immunogenic [148].

Adamantinomatous craniopharyngiomas

In the case of *CTNNB1* mutations**,** there is no specific targeted therapy. Recently, an encouraging clinical trial conducted in patients with desmoid tumors, in which pathogenic signaling pathways involve beta catenin, could pave the way for therapies such as nirogacestat in ACP[149]. The results discussed below are based on isolated clinical observations.

- ***MEK inhibitors***

Trametinib has shown promising results [71,150,151]. Binimetinib, 45mg b.i.d. resulted in initial tumor shrinkage over 8 months and prolonged stabilization in a young woman with multi-recurrent ACP [151]. Clinical tolerance was problematic, with a need for dose reduction (30mg morning and 15mg evening) and a therapeutic pause due to skin toxicity, hyponatremia, venous stasis, asthenia and weight gain. One clinical trial is currently recruiting for this treatment (NCT05286788).

- ***IL-6 and VEGF inhibitors***

Tocilizumab (anti-IL6 receptor) has recently been used in two young patients with recurrent cystic ACP in compassionate use, after failure of local cystic treatment either as monotherapy (n=1, aged 7 years) or in combination with bevacizumab (n= 1, aged 3 years) [152]. Both patients showed an increase in cystic IL6 concentration. Treatment (tocilizumab 12mg/kg iv every 2 weeks) was clinically and morphologically effective, particularly in the cystic portion, and generally well-tolerated, apart from an asymptomatic grade 3 neutropenia in the child treated with dual therapy. In this child, bevacizumab was added in 2nd intention after 6 months' stabilization on monotherapy due to signs of recurrence on MRI. He was treated for 14 of the 28 months of follow-up, with breaks in treatment. The 2nd child treated with tocilizumab alone was treated for 7 months with a partial response and no toxicity. The duration of follow-up after cessation of treatment is not known, although this information is essential to assess the risk of rebound after cessation of treatment, as described in gliomas. There are currently two clinical trials recruiting patients to test tocilizumab in ACP (NCT03970226 and NCT05233397). Blocking the VEGF pathway has been tested in adults with ACP with efficacy observed only for the cystic component[153]. Side effects described have been moderate, these being infections, neutropenia, thrombocytopenia, and hepatic cytolysis.

- ***Anti-PD1 / anti-PD-L1 drug treatments***

Multicenter studies with analysis of clinical, radiological, histological, and molecular data are needed to define the place of these drugs in the therapeutic strategy for ACP. A case of CP in a 17-year-old patient has been reported in the literature (Nivolumab monotherapy) showing no efficacy [154]. To date, there are no data on the potential efficacy of immunotherapies targeting PD1 or PD-L1, however one clinical trial in its recruitment phase is testing nivolumab and tovorafenib in combination (NCT05465174).

Papillary craniopharyngiomas

Published studies on the efficacy of targeted therapies in PCP are encouraging.
Mutation of the *BRAF* gene (V600E) is present in 95% of cases of PCP [65]. As in other cancers with *BRAF* hotspot mutations, the combination of BRAF and MEK inhibitors (trametinib or cobimetinib) is recommended to improve tolerability, reduce the risk of secondary skin cancers, reduce the risk of resistance, and increase anti-tumoral efficacy. These treatments have been tried mainly in recurrent tumors, and very rarely in the neoadjuvant setting for tumor reduction. A recent phase 2 study evaluated the efficacy of vemurafenib-cobimetinib in combination (administered in 28-day cycles) in patients with ACP, with an objective response observed in 15 out of 16 patients [155]. Although no progression was observed under treatment, 3 patients experienced recurrence after treatment was stopped. Other MEK/BRAK inhibitors in combination have been tested[156]. Side effects described in this study included skin rashes, hyperglycemia and increased CPK enzymes, necessitating discontinuation of treatment (19%). Minor side effects were also described including frequent mild-to-moderate fever; frequent arthralgias; 1 patient with cytolysis, and photosensitivity. Another Phase II study is currently underway with dabrafenib/trametinib in combination (NCT05525273). These data have changed the paradigm of the therapeutic strategy for PCP considerably [157]. Whenever possible, patients should be included in clinical trials for these treatments.

Intracystic treatment of craniopharyngiomas

- *Treatments with intracystic chemo-/radiotherapy cannot be recommended outside of study protocols, particularly in view of the irreversible neurotoxicity that may result (strong).*

In cystic ACPs, local treatments have been proposed, particularly in children, to delay radiotherapy. The therapies used have been either interferon-α (IFN α), local radiotherapy ($Yttrium^{90}$ or $Phosphorus^{32}$), or chemotherapy molecules (bleomycin)[3]. Treatment with intracystic IFN α is effective on cystic but not solid portions of the tumor [158,159]. Intracystic chemotherapy with bleomycin has also shown some efficacy in small series [160,161]. However, a more recent study failed to confirm this efficacy, and the treatment has been associated with neurotoxicity[162]. Published data almost exclusively concern children: in the review by Mrowczynski *et al.*, only 12 adult cases had been treated with bleomycin, compared with over a hundred cases in children [158]. In the same review, no adults were treated with IFN α. Thus, studies of intracystic treatments for CP are of low power, mainly concern children, and do not permit a reliable assessment of the risk-benefit balance. These treatments cannot therefore be recommended outside study protocols, particularly in view of the irreversible neurotoxicity that may occur.

CRANIOPHARYNGIOMA-ASSOCIATED COMORBIDITIES

Endocrine deficiencies in the immediate post-operative period

- *Endocrine deficits observed after surgical resection of a craniopharyngioma should be considered as endocrine consequences of surgery, rather than post-operative complications (strong).*
- *Concerted post-operative follow-up with an endocrinology team with expertise in pituitary pathology is recommended, regardless of the type of surgery (strong).*
- *Besides clinical assessment (quantification of fluid intake, weight, and diuresis), the following assays are recommended: plasma cortisol (8 am if the context allows it), natremia/natriuresis, plasma and urine osmolality (strong).*

- *Prevention of both corticotropic insufficiency (administration of hydrocortisone) and dehydration (access to water) are of paramount importance (strong).*

In children and adults, early hormonal assessment is required, with plasma cortisol levels measured as a priority (preferably at 8 am).
The seven day plasma half-life of fT4 suggests that the immediate post-operative thyroid work-up should be analyzed with caution, as there is a risk of underestimating the existence and depth of a thyrotroph deficiency of recent onset. Nevertheless, fT4 measurement remains of interest to establish the existence of a preoperative thyrotroph deficit that may have worsened.
The search for AVP-D (formerly central diabetes insipidus) should be carried out immediately in the post-operative period, based on clinical assessment (weight and quantification of fluid intake and diuresis). It is important to stress that water deprivation test is contra-indicated in this case.

- In children, hydro-electrolyte balancing in the post-operative period is sometimes tricky and requires knowledge of the child's previous weight and current weight, total oral and intravenous water intake, diuresis, natremia, plasma and urine osmolality in the immediate post-operative period, and then initially every 4 to 8 hours.
- Conscious patients must have free access to water during this critical period. Paraclinical monitoring is based on measurement of natremia, natriuresis, plasma and urine osmolalities and urine specific gravity[163]. There are no data in the literature showing a difference in the drug treatment (desmopressin) of AVP-D in adults between CP and other etiologies (apart from adipsic diabetes insipidus, see Box 3).

A triphasic evolution of natremia disorders may occur, with a phase of early postoperative AVP-D (D0 to D3/D5), followed by a phase of syndrome of inappropriate antidiuresis (SIAD), then permanent AVP-D [164–166]. Management of SIAD is based on rapid discontinuation of desmopressin (which may have been introduced in the immediate postoperative period), combined with fluid restriction or, more rarely, infusion of 3% hypertonic saline in the event of severe symptomatic hyponatremia. Rare reports of salt loss syndrome (exceptional in adults [167]) have been reported postoperatively in children, combining dehydration, hyponatremia with normal or slightly increased diuresis and inadequate natriuresis (*cerebral salt wasting*). Treatment is based on intravenous saline infusion in cases of severe or symptomatic hyponatremia, carried out in an intensive care unit. Finally, perioperative management of AVP-D often requires close collaboration between endocrinologists and anaesthetists. The management of endocrine deficiencies in the follow up period is summarized in the dedicated section.

Box 3. The specific case of adipsic diabetes insipidus

- Adipsic diabetes insipidus (ADI) is defined as a reduced or absent sensation of thirst, as assessed by a visual analog thirst scale [168].
- The natremia threshold proposed in the literature is 150 mmol/L (in practice, ADI is suspected where natraemia is ≥ 145 mmol/L).
- Management of ADI requires knowledge of the patient weight in the normo-natremic period, which corresponds to the target weight [169,170].
- It relies on daily monitoring of weight, fluid intake, 24-hour diuresis and natremia.
- **In adults**, the aim of desmopressin titration is to achieve a diuresis of 1.5 to 2 liters per day with constant water intake, the water intake being adapted to maintain the target weight (- 0.5 kg of weight in normo-natremia = + 500 ml of water).
- **In children**, the aim of desmopressin titration is to achieve a diuresis of 20-100 ml/kg/d in infants, 20-50 ml/kg/d in children over 2 years of age, with constant *per os* intakes corresponding to physiological water requirements for weight and age.

Metabolic complications

Hypothalamic obesity

- *Patients and their families must be warned of the risk of postoperative weight gain, and directed towards expert centres that offer conditions for preventing the development or worsening of hypothalamic obesity and eating disorders (strong).*
- *Eating behaviour in patients with craniopharyngioma should be systematically evaluated with adequate tools (weak).*
- *Early therapeutic intervention combining dietary advice and support for eating disorders is recommended as early as the immediate post-operative period (strong).*
- *The occurrence of digestive disorders (particularly vomiting) in patients receiving pharmacological treatment for hypothalamic obesity should result in adaptation of hydrocortisone dose to avoid corticotropic insufficiency (strong).*
- *Bariatric surgery may be an alternative option in the management of obesity secondary to craniopharyngioma in children or adolescents. It must be discussed by a multidisciplinary committee and supervised by a multidisciplinary team including endocrinologists (strong).*

One of the most important long-term side effects of CP and its treatment is weight gain and the development of obesity, known as hypothalamic obesity (HOb). HOb has a major negative impact on health, quality of life and self-esteem[171]. This stigmatization contributes to the worsening of obesity in childhood, to difficulties in social integration and to the worsening of obesity-related comorbidities[172]. At the time of CP diagnosis, the prevalence of HOb varies between 4% and 15%. After treatment, HOb becomes more frequent, especially in children, with a prevalence that can exceed 50% [171]. Weight gain occurs mainly in the first year or even the first 6 months after treatment, usually followed by a plateau phase [173]. However, continuous weight gain is also possible.

Risk factors for HOb include the degree of hypothalamic involvement at diagnosis, preoperative body mass index (BMI), young age at diagnosis, dosimetry received in radiotherapy and extent of surgery/degree of hypothalamic involvement postoperatively[3,173,174]. When CP occurs at a pediatric age, overweight or obesity is present in 25% of cases[85]. The largest registry of children with CP in Germany reported that the mean BMI gain at diagnosis was 0.8 ± 2 SD score compared with a reference population, the mean BMI gain was 3 ± 2 SD score within 3 years in cases of hypothalamic involvement, and there was an additional BMI gain of 1.5 ± 2 SD score over the following 7 years [25,175].

The pathophysiology of HOb is complex. Hypothalamic damage alters the homeostatic regulation of energy intake, leading to hyperphagia, while the imbalance in the sympatho-vagal balance leads to hyperinsulinism. Hyperphagia, decreased resting energy expenditure and reduced physical activity leading to HOb are worsened by the coexistence of altered sleep-wake rhythms, sleep disorders and neuropsychological disorders. Inadequate replacement of pituitary deficiencies may worsen the condition[171,176–179]. Notably, an oxytocin deficit may be involved in the pathophysiology of obesity and dysautonomia and, possibly, in metabolic issues[180].

There is no specific treatment for CP-related HOb, however GLP1 analogs used in common obesity have been the subject of randomized controlled trials in HOb[181,182]. Hypothalamic involvement does not appear to be a brake on the efficacy of these molecules[183]. Setmelanotide, a melanocortin type 4 receptor agonist, also showed promising results in HOb[184]. Side effects are the same as those encountered in populations suffering from common obesity treated with GLP1 analogs, or genetic obesity treated with setmelanotide. In this latter group, hyperpigmentation is a common side effect[184]. Particular attention should be paid to patients suffering from endocrine deficiencies (particularly corticotropic deficiency) who experience digestive side effects with either GLP1 analogs or setmelanotide.

Bariatric surgery has been reported to be less efficient than in common obesity [185],[186]. Although no adverse events specific to CP have been reported, particularly concerning postoperative hormone replacement therapy, its indication must be discussed in a case-by-case approach.

Obesity-related metabolic comorbidities

- *Systematic screening for Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD), and hepatic fibrosis, is recommended in all adults with craniopharyngioma (strong).*
- *Dyslipidemia and diabetes should be screened for in any patient ≥ 15 years old with a craniopharyngioma (strong).*
- *Dyslipidemia, diabetes and MAFLD should be screened for in all obese children and adolescents with craniopharyngioma (strong).*

- ***Metabolic dysfunction-Associated Fatty Liver Disease (MAFLD)***

Few studies have looked at the prevalence of MAFLD in patients with craniopharyngioma, even though they may have risk factors such as obesity, metabolic syndrome and type 2 diabetes. The prevalence of MAFLD appears to be greater in cases of growth hormone deficiency [187,188]. It has also been shown that the severity of MAFLD correlates negatively with GH levels after adjustment for BMI, and that severe GH deficiency is associated with more advanced MAFLD [189]. One study, of 19 adult CP patients with hypothalamic involvement since childhood, showed a prevalence of MAFLD on CT scan of 50% [190].

- ***Dyslipidemia***

Studies comparing subjects with CP to an age-, sex- and BMI-matched control group showed significantly lower HDL-c levels [27,191,192] and significantly higher triglyceride (TG) levels[192] *a fortiori* when diagnosed during adulthood[193]. As such, current recommendations for the management of dyslipidemia can be applied to patients with CP[194].

- ***Diabetes***

The prevalence of diabetes appears to be much higher than would be expected in relation to obesity levels, such that it affects 10-20% of adults undergoing CP surgery. The standardized incidence ratio is between 4 and 6 [195].
When diabetes is 3 to 6 times more common in adults diagnosed with CP in childhood [5,15]. Diabetes should be managed in accordance with guidelines of the American Diabetes Association, with objectives as strict as for any other patient, with an annual check-up of diabetic complications in adults[196]. Preference should be given to weight-loss boosting therapies (biguanides, iSGLT2, and especially GLP-1 agonists) on the basis of specialist advice. It is essential that patients should have a regular adapted physical activity and resistance exercise program.

Hypothalamic syndrome (excluding hypothalamic obesity)

Hypothalamic syndrome encompasses all manifestations linked to hypothalamic destruction by the tumor itself and/or by its treatment(s) (surgery, radiotherapy). These manifestations include obesity, endocrine deficits, dysautonomic disorders (regulation of temperature, thirst, sweating), neuropsychological disorders and sleep disorders. Van Santen *et al.* have recently proposed diagnostic criteria for hypothalamic syndrome in children, with a score enabling early detection of these manifestations and hence rapid management [197]. Overall, around 50% of CP patients present with hypothalamic syndrome[197]. Symptoms of hypothalamic syndrome should be sought during clinical follow-up of patients, and objective assessment (study of cardiac variability, temperature measurement, calorimetric evaluation of resting energy expenditure, physical activity questionnaires) should be carried out during long-term follow-up of patients.

Sleep disorders

- *Screening for sleep disorders should be systematic in patients with craniopharyngioma after therapeutic management (surgery, radiotherapy) with appropriate tools (strong).*
- *Signs suggestive of narcolepsy or secondary hypersomnia should be referred to expert sleep centers (weak).*

As many as 25% to 100% of patients with CP complain about hypersomnolence, 14 to 35% complain of secondary narcolepsy, and 4 to 46% of sleep apnea. Sleep disorders in patients with CP

are multifactorial, with possible alteration of the hypocretin (= orexin) system, abnormal secretion of orexin leading to secondary narcolepsy, obesity favoring upper airway obstruction during sleep, and thus sleep apnea syndrome (with related complaints of non-recuperative sleep and hypersomnolence). Alteration in circadian rhythms, with reduced melatonin production (further increased in the case of visual disorders), also contribute to changes in sleep-wake rhythms and complaints of hypersomnolence and insomnia.

The management of sleep disorders is crucial, since they are closely linked to cardiovascular, metabolic and psychiatric health (anxiety and depression), as well as to immune and cognitive system function[198–200]. In the event of pathological scores on questionnaires, or signs suggestive of sleep apnea syndrome (complaints of hypersomnolence, non-recuperative sleep, intense and frequent snoring, sensations of nocturnal suffocation, respiratory pauses observed by family and friends), ventilatory polygraphy or even nocturnal polysomnography should be performed.

Abnormal circadian rhythms

- *In patients with craniopharyngioma, it is recommended to maintain regular exposure to daylight during the day and avoid excessive exposure to artificial light (including blue light at night, avoid nocturnal food intake which desynchronizes peripheral clocks and could favor metabolic disorders (weak).*

Circadian rhythms are endogenous rhythms that enable us to anticipate recurrent changes linked to the alternation of day and night. A central clock is located in the suprachiasmatic nuclei (SCN) of the hypothalamus, directly above the optic chiasm [201]. The rhythms of this clock, spontaneously of ≈24 h, are synchronized to the local schedule by light perception through photoreceptors (retinal ganglion cells containing a specific pigment, melanopsin) that project to the SCN [202]. The latter communicates with other hypothalamic nuclei and the epiphysis to modulate body temperature and the production of hormones such as cortisol and melatonin, themselves enabling 24-hour physiological adaptations. Pre-clinical models have demonstrated the importance of the central clock, for example that anatomical damage of the SCN abolishes physiological and behavioral circadian rhythms [203]. Pre-clinical data thus suggest that craniopharyngioma or its treatments (resection and radiotherapy) may have clinical consequences linked to the alteration or loss of central circadian rhythms[204]. These may include daytime hypersomnolence that persists despite hormone replacement and treatment of obstructive sleep apnea.

Neuropsychological disorders

- *In children and adults, a thorough neuropsychological evaluation is recommended firstly at the time of diagnosis of craniopharyngioma, and then at a later stage, depending on the patient's age at the time of diagnosis, the treatments received and the patient's clinical complaints (strong).*

Patients with CP can develop neuropsychological disorders, which are mainly observed after treatment, and can occur at any age at diagnosis of CP. These disorders can be classified into six categories and are listed below in order of frequency[121].

1. Memory disorders (working memory, long-term memory, working speed).
2. Behavioral changes/personality shifts or even emotional indifference.
3. Emotional disorders including apathy and irritability/agitation.
4. Cognitive impairment, generally mild to moderate.
5. Altered mood, including hypomania and depression.
6. Delirium/hallucinations.

It should be stressed that there is currently **no evidence that intelligence quotient is worsened in case of craniopharyngioma**[205]. As such, IQ must be considered normal in patients with CP.

Neuropsychological disorders are of multifactorial origin: hypothalamic invasion with extension to V3 may be associated with a reduction in the volume of white and grey matter within the limbic system

involved in higher functions (cognitive, mnesic and executive functions), pituitary hormonal deficiencies, extensive hypothalamic surgery (particularly in the case of multiple recurrences), and radiotherapy (particularly high dose and/or applied to the temporal lobes and hippocampi in children).

In adults, the functions to be assessed in the neuropsychological workup should include: (i) Attention, including psychomotor speed and selective attention, (ii) Episodic memory, (iii) Working memory, (iv) Executive functions (flexibility, inhibition, planning), and (v) Thymia (anxiety, depression).

In children and adolescents, the functions to be assessed in the neuropsychological workup should include, as a priority: (i) intellectual efficiency, including processing speed (WPPSI/WISC, depending on age), (ii) executive functions: flexibility, inhibition, planning, working memory (from age 6), (iii) attentional functions : selective, divided, sustained (from age 6), (iv) psycho-pathological aspects (anxiety, depression) (questionnaires from age 6 + clinical signs) (v) Depending on complaints and clinical observations, psycho-social skills (from age 6), visual gnosias (from age 6) may also be assessed.

Fractionated stereotactic radiotherapy and proton therapy are thought to present a lesser risk to deterioration of these neurocognitive functions. Thymic disorders appear to be more frequent in patients diagnosed with CP in adulthood [206–210]. A reduction in the volume of grey matter of the anterior and posterior limbic systems and in the white matter of the pathways connecting with other areas of the limbic system have been described on MRI. Similarly, different recruitment of fronto-limbic brain regions has been observed on functional MRI during face recognition[211]. This suggests that hypothalamic damage has an impact on neural memory retrieval systems in the medial prefrontal cortex, indicating less efficient use of an area involved in control processes. Correlations have been established between cognitive disorders and abnormalities of the fronto-limbic system on MRI, the latter being involved in the "default mode" network[212,213]. The tests and scales used may vary according to age, socio-cultural level and any visual or hearing impairments. Screening and treatment of these neuropsychological disorders (psychotherapy, speech therapy, psychomotricity, adapted orientation/life project) is essential to limit their impact on quality of life (physical, social and fatigue domains) and to avoid a self-perpetuating cycle (thymic disorders leading to cognitive disorders and vice versa).

MEDICAL AND SOCIAL CARE

- *Quality of life should be systematically assessed using validated scales and questionnaires in all patients with craniopharyngioma. The surgical decision is decisive in limiting the consequences of surgery on quality of life (strong).*
- *For children, multi-professional care involves a neuropediatrician and, if possible, a pediatrician specialized in physical medicine and rehabilitation at the hospital and/or within medical-educational structures (strong).*
- *The need for a person to accompany a disabled pupil (school/student life assistant) must be systematically assessed (strong).*
- *We recommend patients who have undergone extensive surgery to be referred to a physical medicine and rehabilitation unit dedicated to cerebral palsy patients, particularly in the case of severe cognitive sequelae (strong).*
- *A comprehensive approach, involving government departments and their regional/federal delegates, is recommended to facilitate the medical and social care of craniopharyngioma patients (strong).*

The medico-social dimension for child and adult CP patients is of fundamental importance, as it conditions the patient's and family's long-term experience of the pathology and its mostly irreversible consequences[214]. In children, as in adults, the psycho-medico-social consequences of CP have mainly been studied longitudinally, after surgery and/or radiotherapy. Two international registries have shed light on the medico-social consequences of CP: the German KRANIOPHARYNGEOM [215] and data from the KIMS [216].

For children, medical and social care must ensure the best possible conditions for integration into school and society, access to education and personal fulfilment, taking into account physical (endocrinological, visual) and behavioral disabilities.

Impact on quality of life and functional capacity

The impact of CP treatment on quality of life is undeniable, regardless of the age at diagnosis (child, adolescent, adult). A prospective comparative study carried out in 2004, using questionnaires, quality of life scales and specific measures (Youth Self Report, Child Behavior Checklist, PedQOL) for children and their parents, highlighted a clear deterioration in the quality of life of children with CP compared with their controls [217]. Functional abilities, on its various dimensions (i.e., physical ability, degrees of autonomy, emotional functioning, cognitive ability, friendly and family sociability, body image) are severely impaired in CP patients compared with the general population, and directly correlated with worsening BMI [215]. Similar studies have emphasized the importance of hypothalamic invasion and a retrochiasmatic localization of CP as predictive factors of the extent of postoperative impairment of quality of life [218,219]. Likewise, extensive surgery was associated with an increased risk of psychosocial deterioration [33]. A recent study, carried out on a large series of 709 patients, showed that quality of life scores and body image were significantly better in patients diagnosed before the age of 6 than in those diagnosed after this age [220]. Functional skills measured at 5 years were, however, more impaired in younger patients. These results suggest that a diagnosis of CP in early childhood encourages the patient to adapt early to the resulting handicaps, or to have a lower perception of body image deterioration than children diagnosed at an older age. In adults, the study by Patel *et al.* shows that quality of life after CP surgery deteriorates markedly if visual disorders and/or endocrine deficits are present post-operatively[221]. Growth hormone replacement in adult patients with endocrine deficiencies has shown conflicting results in terms of improved quality of life [222,223]. In a study comparing 29 CP adult patients in remission with 142 controls, all aspects of quality of life continued to show a negative impact (general fatigue, physical fatigue, energy, physical condition and physical mobility)[224]. Independent predictive factors for impaired quality of life were the existence of visual disorders, female gender, repeated CP surgery and recourse to radiotherapy.

Impact on emotions and cognitive functions

Craniopharyngioma, and its treatment, has a persistent negative impact on various cognitive, thymic, and executive spheres in patients. In children, behavioral difficulties have been noted in the aftermath (mean follow-up of 6.8 years) of surgery for CP[219]. These were characterized by attention difficulties, social difficulties, and a tendency to internalize, especially in the school environment. However, no significant impairment in IQ has been reported [205]. The emotional impact is perceived to be greater for adolescents and parents. These negative impacts are also related to the altered sleep quality described in patients with CP [225].

In adults, 75% of patients will show a reduction in neurocognitive capacity following surgery, with, in particular, the onset of attention disorders, a deterioration in immediate task performance and short-term memory, or a more marked tendency towards apathy [226,227].

Impact on social integration, emotional and marital life

Adult CP patients have a lower standard of living than the general population. A recent study comparing 59 CP patients (mean age 25 years) with 306 matched patients with type 1 diabetes found a significantly higher proportion of CP patients living with their parents (43% vs. 14%) [228]. Similarly, adult CP patients were less likely to have a driver's license [25]. Occupational health physicians, in consultation with other professionals, play a central role in guiding and advising patients in their applications for employment, reclassification or their job retention.

Finally, various studies suggest a higher proportion of unmarried subjects and increased incidence of sexual disorders in adult patients with CP [25,228,229]. A recent French survey of a sample of 107 patients and their relatives reported an impact of CP on the family or marital sphere in 85% of cases (personal data of TC and B.G-C).

Unmet needs and medico-social actions

Several measures are needed to support CP patients over the long term, with the aim of optimizing their medical treatment and social integration.

The assistance of a social worker may be required for certain procedures, carried out by the patient's attending physician and specialist. Social workers may be required in every facet of community life (schools, hospitals, mental health clinic).
In children, the following social measures may be required:

- The pediatrician or the attending physician should be responsible for ensuring access to care, regardless of the patient's resources. Depending on the country, several measures are in place to enable an allowance or full coverage of medical expenses, for example Disability Benefits provided by Social Security in USA, “Affection Longue Durée” in France, and UK Disability Allowance in the UK.
- There is a need for implementation of a personalized school enrolment program. In many schools (secondary and higher education), there are disability coordinators to facilitate the orientation of children and teenagers concerned.

In adults, the social aspects may include:

- Health cover for long-term illness by the attending physician, to guarantee access to care regardless of resources.
- Care provided by mobile physical and rehabilitation medicine teams, socio-professional assessment with the help of a social worker and occupational physicians.
- Social support services for disabled adults (assistance to help disabled people to achieve their life goals)
- For patients with persistent visual problems, follow-up in a dedicated low vision outpatient clinic.
- The possibility to refer the patient to Acquired Brain Disorders Services that offer a wide range of support and services to the patient within their own communities.
- The support provided by the Patients’ association.

TRANSITION FROM CHILDREN-ADULT AND PREGNANCY

Transition

- *Continuity of care between childhood and adulthood, through a multidisciplinary transition, is essential (strong).*
- *Induction of puberty is based on estrogen therapy in girls, and androgen therapy in boys. Pubertal induction with rhCG and rhFSH may be proposed in boys to enable testicular development, induction of spermatogenesis and sperm preservation could even be suggested (strong).*
- *An assessment of cognitive and memory functions should be offered at transition, to enable the best socio-professional orientation (strong).*
- *At the time of transition, young patients need to be able to understand and explain their illness, their treatment, and the importance of long-term follow-up. Therapeutic education plays a fundamental role in this period (strong).*

Comprehensive, personalized care for young patients must be based on discussion, taking their emotions into account, and adapting to their priorities and lifestyle, with the establishment of specialized input involving adolescent, pediatric and adult endocrinologists. Continuity of care between childhood and adulthood, through a multidisciplinary transition, is essential. Follow-up goals during the transition include monitoring of the tumor, visual impairment, hypothalamic and pituitary endocrine impairment, cardiometabolic comorbidities and neuropsychological disorders/behavior[18].
Management at the time of transition should include:

- Tumor treatment: monitoring after the first neurosurgery is essential. In the presence of tumor residue, "neurosurgical transition" is essential. In the case of radiotherapy, prolonged monitoring of potential long-term sequelae will be necessary [130].
- The existence of visual and neurological sequelae: Visual consequences also require ongoing neuro-ophthalmological care. Their evolution after initial treatment is unpredictable, especially in the case of multiple repeat surgeries [217].
- Pituitary deficiencies: supplementation with somatotropin, levothyroxine, hydrocortisone, and desmopressin follows the same principles in adolescents as in adults.
- Comorbidities: management of overweight/obesity, in particular.

The adult height achieved with growth hormone treatment is generally in line with the genetic target height, with standard doses of growth hormone (often less than 30 µg/kg/day).
Once adult height has been reached, growth hormone has a proven safety profile, and remains useful for acquiring peak bone mass and optimizing body composition in young adults [230,231].
Puberty should be induced at normal physiological age [232–234]. In girls, estrogen should be prescribed in progressively increasing doses, preferably using transdermal 17 beta-estradiol to avoid first-pass hepatic effects. A progestin (preferably natural progesterone) should be added after around 2 years of estrogen therapy, or as soon as the first menstruation occurs.
In boys, pubertal induction should be based on delayed-release testosterone, administered intramuscularly or subcutaneously (testosterone enanthate) in gradually increasing doses over 2 to 3 years, enabling development of the penis and secondary sexual characteristics. However, this treatment cannot increase testicular volume or induce spermatogenesis. To achieve this goal, pubertal induction with recombinant choriogonadotropin alfa (rhCG) and recombinant FSH (rhFSH) delivered by subcutaneous injections (i.e. 3-4 injections per week) may be preferable, as it stimulates spermatogenesis while enabling preservation of sperm. This option should be discussed in the light of the adolescent's maturity and the constraints of multiple injections.
Recombinant FSH is approved in men for the stimulation of spermatogenesis. As a rule, fertility induction is not problematic, as the gonadotropic deficiency is acquired (and therefore the phases of physiological gonadotropic activation in the ante-natal period and during mini-puberty have indeed taken place, associated with the multiplication of Sertoli cells, and without any alteration of germ cells).
Transition is a key period for preventing or treating overweight/obesity associated with hypothalamic syndrome. Multidisciplinary management, particularly of nutrition, and promotion of physical activity, is essential. Neurocognitive outcomes, quality of life and psychosocial outcomes should also be part of the patient's care during the transition. Assessment of cognitive, executive and memory functions should be carried out to propose targeted rehabilitation, and, for young adults, help with integration into socio-professional life. Increased anxiety and reduced self-esteem should also be investigated during this period, and may warrant specialized follow-up and psychological care [91,227,235].
At the time of transition, young patients need to be able to understand and explain their disease, their treatment, and the importance of long-term follow-up: these elements are important to ensure compliance with follow-up and treatment in adulthood, and to avoid breaks in follow-up and the medical or tumor-related consequences these could entail. Therapeutic education structures play a crucial role in empowering young patients.

Pregnancy in women with craniopharyngioma

Gonadotroph deficiency affects up to 29 -74% of adult patients at diagnosis, and 57% to 94% after craniopharyngioma treatment[46].

In women, replacement therapy should consider the presence of overweight or obesity, as well as arterial and venous vascular risk factors, when choosing treatments. The transdermal route is preferred for estrogen intake. Observations of spontaneous pregnancies in patients who have had CP are rare, due to the frequency of hypogonadism and the lower proportion of sexually active individuals compared to the general population [236]. Observations of tumour growth during pregnancy have been reported. Before any pregnancy, a metabolic, hormonal and tumor evaluation is essential, and the case should be discussed, where the clinical situation is complex, by a multidisciplinary board

attached to a Pituitary Tumor Centre of Excellence. Induction of ovulation aims to achieve mono-ovulation, and is achieved by concomitant administration of FSH and LH during the follicular phase, adapted to the individual response, particularly in cases of obesity [237]. Pulsatile administration of GnRH by pump is ineffective in cases with destruction of pituitary gonadotropic cells (as in intrasellar CP). After ovulation, luteal phase support is required, through repeated injections of hCG or administration of progesterone.
There is currently insufficient data to suggest a preferred mode of delivery. Breastfeeding, when possible, has no effect on the disease. A pre-conception consultation with an obstetrician is advised in cases of severe obesity or other comorbidities.

In women older than the physiological age of menopause (around age 50), estrogen and progesterone, if the uterus is still present, should be considered for hormonal menopause therapy. Its continuation should be discussed with the patient in the light of the risk-benefit balance, particularly in terms of bone health. This would rarely be continued after 60 years of age.

FOLLOW UP AND LONG-TERM MANAGEMENT

Endocrine deficiencies during the follow-up

Prevalence

The prevalence of at least one anterior-pituitary deficit after surgery for a CP varies between 60% and 100% of cases, depending on the study. An English study, which included children and adults, with a 10-year follow-up, showed that the percentage of GH, LH/FSH, ACTH and TSH deficiencies was 80-90%, 90%, 85-90% and 80% respectively, and AVP-D was present in 65 to 75% of patients [37,238,239]. Predictive factors for the occurrence of pituitary deficits postoperatively, such as extent of surgery, adjuvant radiotherapy, or tumor size, are controversial in the literature [19,40,240]. To date, the majority of studies agree that the onset and persistence of long-term endocrine deficiencies are more frequent when the CP is diagnosed during childhood.

When and how to assess hormonal axes during the follow-up.

- *In children and adults, basal hormonal evaluations rely on the assessment of morning cortisol, TSH/fT4 and IGF-1. Assessment of the gonadotropic axis (FSH/LH, estradiol in women, testosterone in men) should only be carried out from the pubertal period onwards (strong).*
- *In children and adults, tumor progression and/or new therapeutic interventions (surgery, radiotherapy) should lead to reassessment of previously intact pituitary function (strong).*
- *Endocrine deficits persist in the long-term follow-up of patients with craniopharyngioma. If the deficit is confirmed, it is not necessary to repeat the dynamic testing of that axis (strong).*
- *To avoid under-/overtreatment, assessment of peripheral hormones is recommended in the follow-up of patients treated with hormonal substitution (fT4 for levothyroxine, testosterone in the case of testosterone injection and IGF-1 for GH substitution) (strong).*

In children and adults, in addition to clinical examination, biochemical monitoring is based on an electrolyte panel and exploration of all pituitary hormones, 1 to 3 months after therapeutic intervention (surgery alone, radiotherapy or surgery + radiotherapy). Monitoring includes morning cortisol, TSH/T4L and IGF-1. In the case of new therapeutic intervention, pituitary deficits not previously present should be looked for. Assessment of the gonadotropic axis (FSH/LH, estradiol in women, testosterone in men) should only be carried out from the pubertal period onwards. LHRH testing is not necessary to confirm gonadotropic deficiency. Before pubertal induction, it may be useful to perform inhibin B assays to assess Sertoli cell function, and AMH (*anti-müllerian hormone)* assays to assess ovarian reserve. It is unclear if a growth hormone stimulation test is necessary to confirm or rule out GH deficiency. In the case of CP, since the probability of GH deficiency is high, a normal IGF1 level does not rule out GH deficiency, and it may be advisable to follow up with a GH stimulation test [241]. Radiation therapy, particularly in the pediatric age group, can expose patients to a late risk of endocrine deficits (with the exception of AVP-D, which is never generated by radiation therapy),

radiation-induced tumours, cognitive disorders and vascular thrombosis [242]. A pre- and post-radiotherapy endocrine assessment is essential, especially if there is no hypothalamic-pituitary deficit prior to irradiation. We recommend a reassessment of intact pituitary hormone functions annually in the long term after radiotherapy.

There is no systematic indication to look for secondary recovery in patient follow-up, *a fortiori* in cases of complete pituitary insufficiency (panhypopituitarism). As such, this aspect can be left to the discretion of the medical team, depending on the context (age of the pituitary deficit, extent of the deficit, single therapy or multiple sequences). However, to avoid under-/overtreatment, assessment of peripheral hormones is recommended in the follow-up of patients treated with hormonal substitution (fT4 for levothyroxine, testosterone the day before the next injection of testosterone enanthate, and IGF-1 for GH substitution, respectively).

Hormonal substitution in the long term

- *In the case of gonadotropic replacement therapy, hormone replacement therapy should be continued in women at least up to the physiological age of menopause. Beyond this age, the risk-benefit balance should be considered when deciding whether to continue treatment. In men, gonadotropic substitution (androgen therapy) can be offered throughout their lives in the absence of contraindications (strong)*
- *In both children and adults, GH treatment should be discontinued in the event of recurrence or progression of craniopharyngioma. Reintroduction of GH treatment, if necessary, should be discussed by a dedicated tumor board (strong)*

There are no major differences in the long-term treatment of corticotroph, thyrotroph and gonadotroph deficiencies in patients with CP compared to treatment in other causes of pituitary deficiencies. Hydrocortisone substitution should be monitored clinically, looking for signs of over- or under-dosing. In craniopharyngioma patients, monitoring is more delicate, due to the asthenia or hypothalamic obesity sometimes associated with hydrocortisone supplementation. For thyrotroph deficiency, the goal is to obtain an fT4 level in the upper third or half of the upper limit of normal. In cases of associated corticotropic deficiency, corticotropic substitution should precede thyrotropic substitution. It should be kept in mind that fT4 levels may fall after replacement of associated somatotropic and/or gonadotropic deficiency(s), necessitating an increase in levothyroxine dosage.

Long-term hormone replacement therapy is important, as it not only improves quality of life and fertility, but also reduces the risk of bone loss and significantly reduces cardiovascular risk [3].

In children, GH treatment may be started as early as 6 months after completion of CP treatment, after verification of disease stability on two successive MRIs spaced 3 months apart, or even as early as the 3rd month in certain children whose growth and BMI have been severely affected.

In adults, the beneficial effects of GH replacement therapy for patients with a history of CP have been debated. Replacement should be introduced after discussion with the patient, consideration of the impact of the deficit and the risk factors inherent to the patient's overall state of health. In general, GH therapy is introduced 1 to 2 years after the last surgery. These data are based on observational, retrospective, non-randomized studies. However, the most recent studies are reassuring. A study from the UK, with a follow-up of 10.8 ± 9.2 years (range 1.9-40 years), showed that GH treatment did not increase the recurrence rate of CP [243]. Olsson *et al.* compared two groups of CP patients treated or not treated with GH (15-year follow-up). They showed that the recurrence rate was identical in both groups. However, the frequency of residual tumor was lower in the GH-treated group (29 vs. 45%), suggesting that the population in this group had been carefully selected [244]. More recently, an Italian study showed no correlation between GH treatment and CP recurrence, in a population including 89 patients with a mean age at inclusion of 35 ± 1.6 years, after a median follow-up of 7 years since the last surgery [245,246]. In the KIMS study published in 2022, 15,809 patients with GH deficiency were treated and followed for a mean of 5 years and a maximum of 18.3 years [247]. Of these patients, 10.6% had a history of CP. The data suggest that GH treatment is safe in terms of recurrence rate and metabolic profile. In both children and adults, GH treatment

should be discontinued in the event of recurrence or progression of CP. Reintroduction of GH treatment, if necessary, should be discussed by a dedicated tumor board.

Long-term compliance with hormone therapy is an important issue. In the study by Cheng *et al.,* only 20% of patients took their prescribed estrogen-progestin or GH therapy over the long term [238]. Long-term hormone replacement therapy is important, as it not only improves quality of life and fertility, but also reduces the risk of bone loss and significantly reduces cardiovascular risk [3]. Patients who have had CP are recommended to undergo lifelong multidisciplinary follow-up at an expert center, especially for assessment of bone fragility. Several studies have found decreased BMD in CP patients [248,249] despite estrogen-progestin hormone replacement therapy and/or GH treatment, and in the absence of excess hydrocortisone substitution. The female population is particularly at risk. Specialized care may therefore be required to consider anti-osteoporotic treatments in addition to HRT, or when HRT is contraindicated.

It should be noted that, to date, there is no evidence that bariatric surgery has a significant impact on the absorption of endocrine replacement therapies [250].

Imaging during follow-up

- *In children, imaging surveillance should be performed every 3 months during the first year, then every 3 to 6 months over the following years. It should become annual only after 5 years of stability, and can be performed every 2 years after 10 years of stability (strong)*
- *In adults, craniopharyngioma patients should be monitored at 3 months and, at the latest, at 12 months post-operatively. For the first 5 years, monitoring should be annual, then every 2 years between 5 and 10 years, and every 3 to 5 years thereafter (strong).*
- *The frequency of monitoring and the expectation of new imaging can be anticipated depending on the context (existing tumor residue, evolution, appearance/recurrence of clinical signs) (strong).*
- *Bone mineral density should be assessed by two-photon bone densitometry, particularly in women, every 3 to 5 years (weak)*

Modalities

Imaging follow-up is based on the measurement of solid and cystic tumor components and their relationship with the visual pathways and hypothalamus [251]. 3D T2 and 3D FLAIR sequences enable better reproducibility of measurements and identification of small remnant images that may go unnoticed on T2 and T1 slice acquisitions.
In the event of radiotherapy, a transient increase in cysts may occur [129]and requires close MRI monitoring during treatment [140].
The recommended acquisition protocol is identical to the post-operative protocol, apart from diffusion:

- T1 spin echo (SE) without and with gadolinium injection
- Coronal T2 thin sections (2 mm), 3D T2 and 3D FLAIR.
- In children and young adults, some teams recommend monitoring without injection, to limit the relative risk of gadolinium accumulation.

Frequency of MRI

In adults, a "standardized" MRI monitoring protocol could be to perform an MRI between 2 and 4 months post-operatively, then at 12 months post-operatively (**Fig 7**). Imaging monitoring may be annual for 5 years, then every 2 years from 5 years onwards. However, the frequency should be adapted on a case-by-case basis, depending on the presence of any residual tumor, its progressive nature, and the appearance or re-emergence of clinical signs.
MRI should be performed as a matter of emergency in the event of new symptoms that suggest progression (unusual headaches, vomiting, visual impairment, deterioration of general condition). Failing this (contraindication to MRI, for example), a brain CT should be performed.

In children, the situation is somewhat different, prompting closer monitoring: as the risk of recurrence is higher in pediatric CP, monitoring is therefore based on MRI scans every 3 months during the first

year, then every 3 to 6 months over the following years, depending on the neurosurgeon's assessment. It should become annual only after 5 years of stability (**Fig 7**).

Bone Mineral Density

Patients with CP are recommended to undergo lifelong multidisciplinary follow-up at an expert center especially for assessing bone fragility. Several studies have found decreased BMD in CP patients [248,249] despite estrogen-progestin hormone replacement therapy and/or GH treatment, and in the absence of excess hydrocortisone substitution. The female population is particularly at risk. Specialized care may therefore be required to consider anti-osteoporotic treatments in addition to hormone replacement therapy, or when HRT is contraindicated. We thus recommend a bone mineral density assessment by two-photon bone densitometry, particularly in women, every 3 to 5 years.

Visual explorations during the follow-up

Neuro-ophthalmological follow-up should be organized according to initial findings. It should include at least one new early assessment (< 3 months) after treatment (surgery and/or radiotherapy) and one more at 12 months. The remaining follow up should be discussed on a case-by-case basis based on the patient's complaints, tumor growth and/or therapeutic intervention that may affect visual functions.

Education program

- *An education program must be offered to children and adult patients with craniopharyngioma and their families (weak).*

One of the aims of an education program is to help patients acquire or maintain the self-care and coping skills they need to manage their lives with a chronic disease, improve their quality of life and achieve their life goals (World Health Organization. Copenhagen: Regional Office for Europe, 1998. Therapeutic patient education).

In pituitary diseases, education programs have recently been developed [252–254]. A recent study focusing on patients with a confirmed diagnosis of pituitary adenoma underlines the importance for patients of being able to obtain appropriate information from a specialist, thereby reducing the anxiety associated with the diagnosis and improving patient satisfaction [254]. In 53 patients, including 4 with CP, a dedicated education program was associated with an improvement in some parameters of their quality of life (physical and psychological limitations), better management coupled with reassurance regarding their pituitary pathology, and overall satisfaction at the end of the program [253]. To date, no program has been developed specifically for CP patients (neither in adult nor in paediatric patients), even though they represent a patient population that could benefit most from such a program in terms of safety (management of panhypopituitarism and its complications), quality of life and social and professional integration. Education programs are also beneficial in breaking patient isolation, by giving them the opportunity to meet other patients suffering from the same rare disease. In the case of adolescents, an education program is a necessary accompaniment to help them adhere to the therapeutic project and take responsibility for their disease.

Patients' relatives also benefit from such programs, with improvements in vitality, anxiety and depressive symptoms. It is also desirable that such education programs should, where possible, involve the relevant patient associations, as well as expert patients.

Recurrence during follow up

Local recurrences of CP are frequent, ranging from 0 to 57%. They may be symptomatic (headaches, visual disturbances) or diagnosed on imaging as part of surveillance [255].

Risk factors for recurrence

The risk of recurrence depends on the treatment strategy. In a study of adult patients with a 3-year follow-up, recurrence was observed in 17% of patients with total resection, 27% with subtotal resection plus radiotherapy and 45% with subtotal resection alone, with no significant difference in the risk of recurrence between total resection and partial resection plus radiotherapy [134]. Recurrence is therefore a common occurrence, even after resection described as complete, and after post-operative imaging showing no residual tumor. The absence of post-operative radiotherapy and the presence of post-operative residue after initial tumor surgery are the most frequently-found predictive markers of recurrence, whether for early recurrence [256] or late recurrence [37]. Pituitary stem conservation appears to reduce the risk of pituitary insufficiency without increasing the risk of recurrence, according to a 2015 meta-analysis [257].

Signs of aggressiveness of the initial tumor, *i.e.* initial size, invasion of the third ventricle, adhesion to adjacent structures, expression of p53, are also associated with an increased risk of recurrence [256]. The risk of recurrence seems to increase with anatomopathological type, according to a recent meta-analysis of 976 patients, with 26% recurrence for ACP and 14% for PCP[258].

Recurrences most often occur within the first 5 years after surgery, but late recurrences are also possible. The average time to recurrence varies from 26 to 96 months, with recurrences sometimes occurring much later, up to 27 years [255]. These times vary according to treatment, with averages of 29.1, 81.3 and 23 months for patients treated by total resection, subtotal resection and radiotherapy, or subtotal resection alone, respectively [134].

Rare cases of ectopic recurrence have been described along the neural axis extending from the subcortical space to the S1 root. A recent review of the literature describes 67 cases of ectopic recurrence, with a disease-free interval of up to 26 years [259]. These recurrences developed either along the surgical pathway or via the CSF. No cases of ectopic recurrence have been described after transsphenoidal surgery.

SUMMARIZING CONCLUSIONS

Overall, the management of craniopharyngiomas, either in children or in adults, remains complex and requires input from several fields of the healthcare system. Recent guidelines about craniopharyngiomas have been published but they only focused on childhood[260]. The aim of this reference document, endorsed by the French Endocrine Society/French Society for Paediatric Endocrinology & Diabetes, is to provide concise, detailed, up-to-date guidelines, from diagnosis to long-term follow-up, for clinicians dealing with patients with craniopharyngiomas.

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	Children		**Adult**	
	Before surgery[a]	*After surgery*[b]	*Before surgery*[a]	*After surgery*[b]
≥ 1 endocrine deficit	54-100%	100%	41-73%	93-99%
ACTH	8-68%	78-97%	35-68%	74-90%
TSH	15-32%	86-98%	35-56%	81-92%
GH	41-100%	77-93%	18-86%	52-68%
LH/FSH	20-56%	59-95%	29-74%	70-94%
AVP-D	7-22%	60-91%	6-21%	43-70%
Panhypopituitarism	3-48%	5-66%	6-18	34-60%

Table 1. Prevalence of endocrine deficits in patients with craniopharyngioma ([a] from references [38,261–263] and [b] from references [37,47,193,261–263])

Figure 1. Summary of the working groups set up to draft the guidelines

Figure 2. Examples of different appearances of adamantinomatous craniopharyngiomas. A: Uniloculated cystic suprasellar lesion with spontaneous T1 hyperintensity, B: Uniloculated cystic suprasellar lesion with enhancing wall. C: Multiloculated suprasellar solid and cystic lesion. D: Calcifications on CT scan.

Figure 3. Papillary craniopharyngioma
Solid and cystic suprasellar mass lesion A) Post contrast coronal T1-weighted image demonstrates the solid enhancing predominant component while B) Coronal T2-weighted image shows a lateral cyst together with peripheral edema.

Figure 4. Assessment of the accurate topography of two different craniopharyngiomas, based on 3D T2 in the sagittal plane.
A: mammillary body (arrow) and floor of the third ventricle are depicted under the lesion (intra-V3)
B: mammillary body (arrow) and floor of the third ventricle are lifted up by the lesion (pseudo-V3).

Figure 5. Histo-molecular workflow for craniopharyngioma diagnosis.
ACP: adamantinomatous craniopharyngioma; **PCP**: papillary craniopharyngioma **IHC**: immunohistochemistry; **WT**: wild-type.
*To be discussed after review by an expert center.

Figure 6. Schematic representation of a craniopharyngioma and possible surgical approaches

Figure 7. Schematic diagram of the follow-up as recommended by the current guidelines, for the management of children and adult patients with craniopharyngiomas.

Figure 1

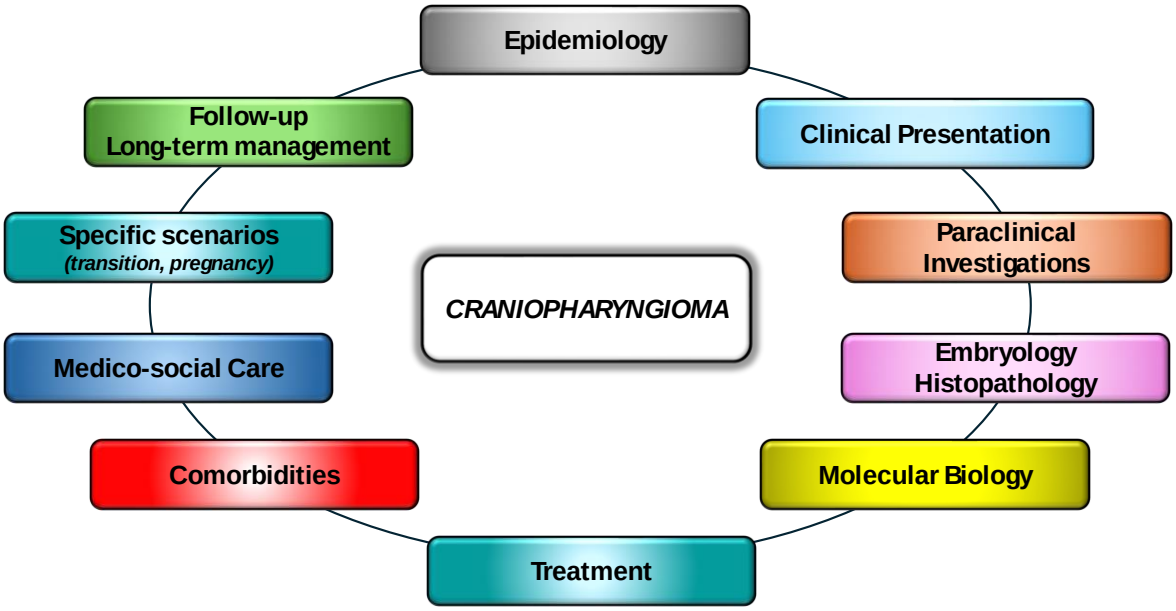

Figure 2

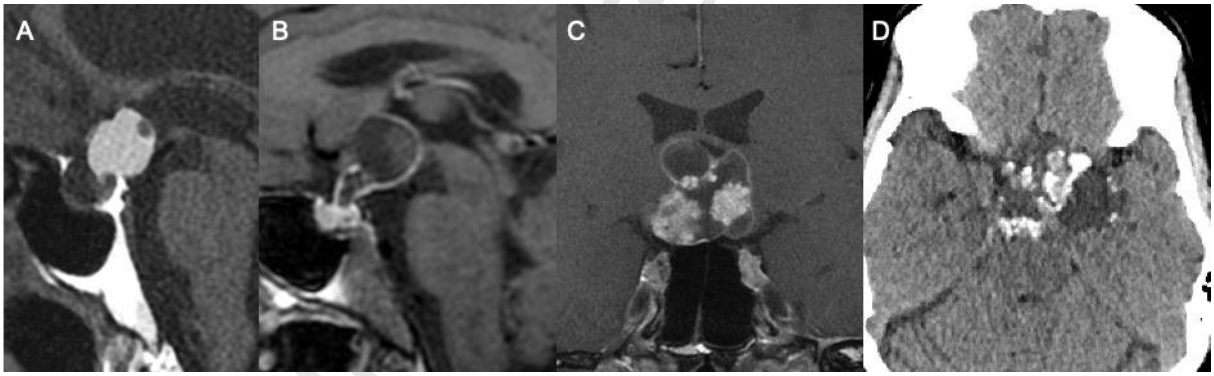

Figure 3

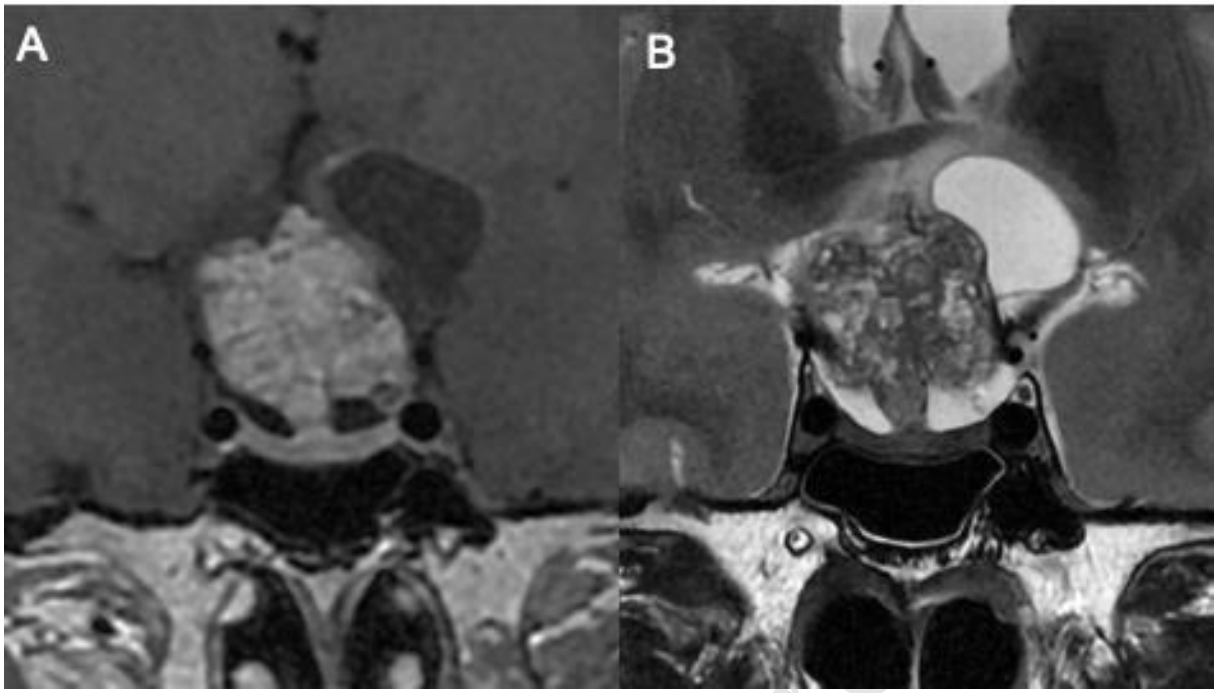

Figure 4

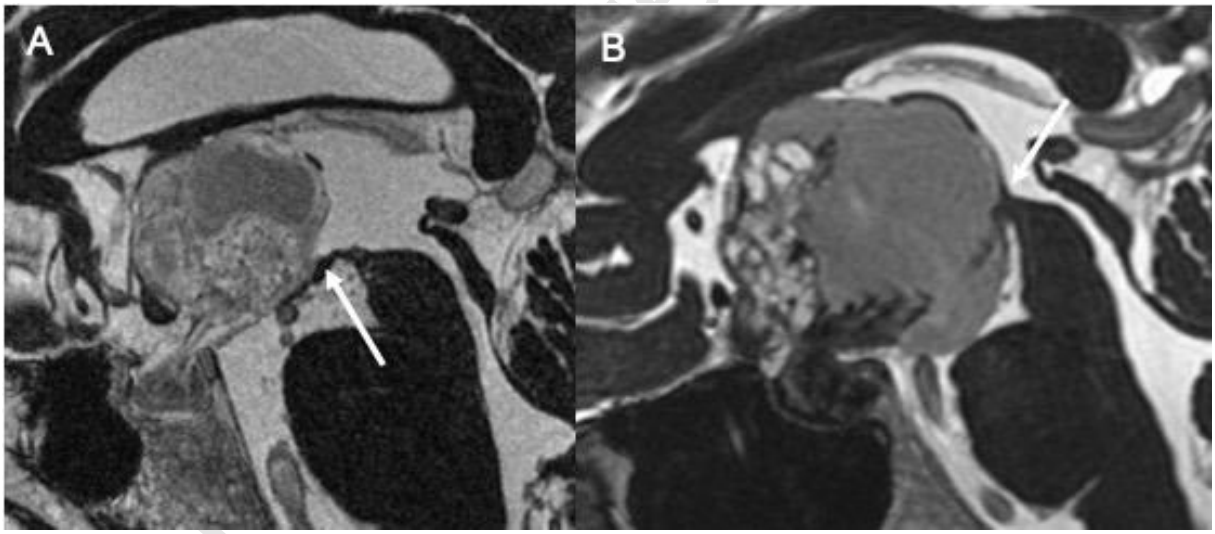

Figure 5

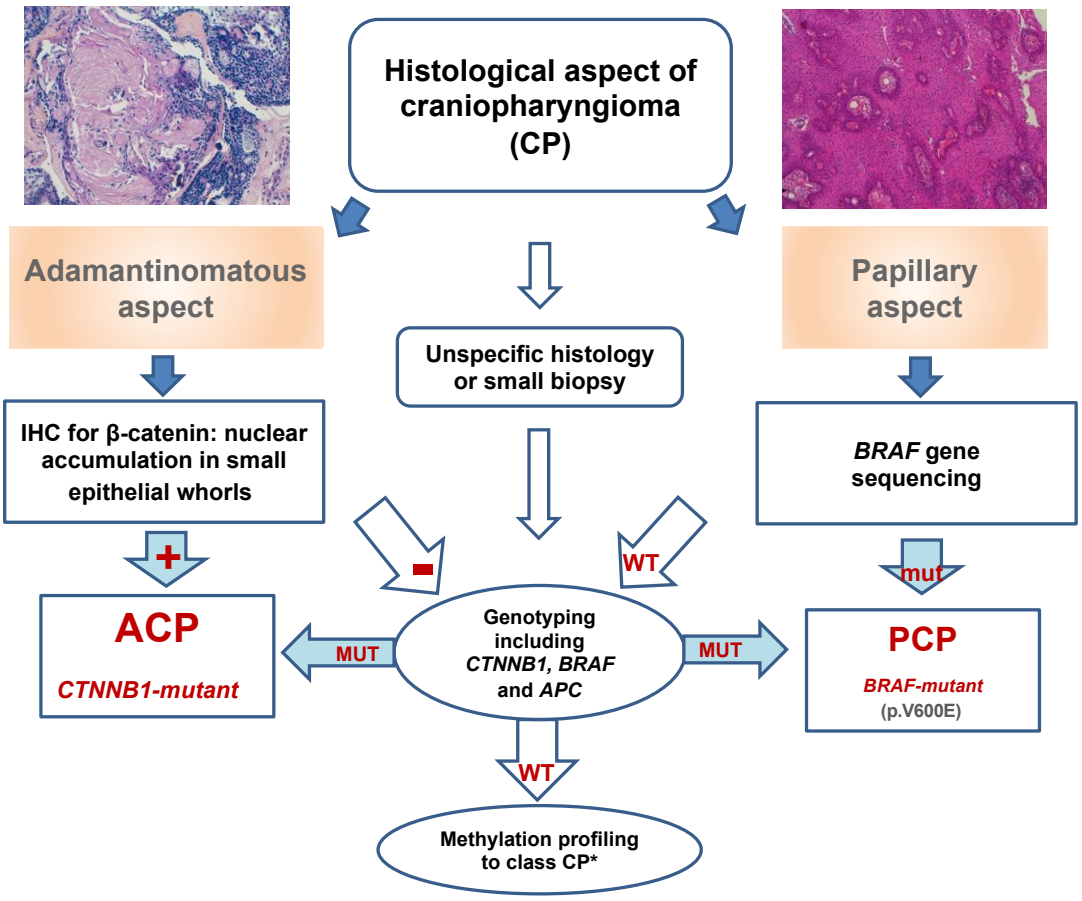
Histological aspect of craniopharyngioma (CP)
Adamantinomatous aspect
Papillary aspect
Unspecific histology or small biopsy
IHC for β-catenin: nuclear accumulation in small epithelial whorls
BRAF gene sequencing
+
-
WT
mut
ACP
CTNNB1-mutant
MUT
Genotyping including CTNNB1, BRAF and APC
MUT
PCP
BRAF-mutant
(p.V600E)
WT
Methylation profiling to class CP*

Figure 6

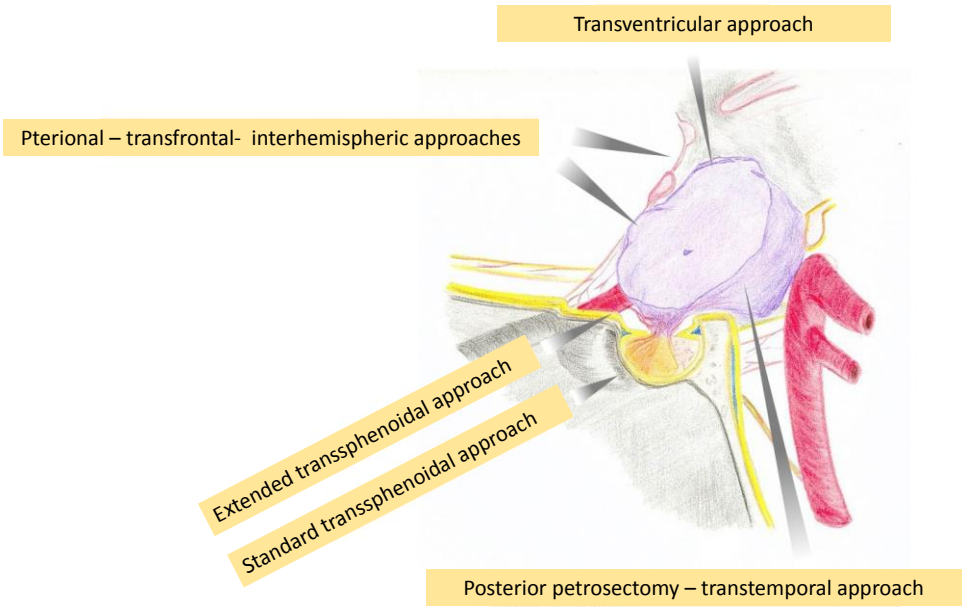
Transventricular approach
Pterional – transfrontal- interhemispheric approaches
Extended transsphenoidal approach
Standard transsphenoidal approach
Posterior petrosectomy – transtemporal approach

Figure 7