CRANIOPHARYNGIOMA
STANDARD CLINICAL PRACTICE RECOMMENDATIONS

The lay-out used in this template may be adjusted to bring the document in line with other disease specific standard clinical practice documents.

General remarks:

The recommendation for brain tumours will finally consist of a general roadmap and nine tumour specific sections for (LGG, HGG, medulloblastoma, rare embryonal tumours, ATRT, ependymoma, GCT, CP, CPT).

The general roadmap includes sections on neurosurgery, neuroradiology, neuropathology, radiotherapy, endocrinology, neuroophthalmology, neuropsychology, and survivorship/ quality of life.

- *Take all international European, national and working group guidelines on your tumour entity into account for this document*
- *Focus only on criteria specific for your tumour entity; general requirements, for example for neurosurgery or radiology, are mentioned in the "general roadmap".*
- *If you have general criteria in mind for different chapters, which you think are important, please add them in a separate section (as bullet points) and they can later be integrated in the general part.*
- *Besides describing what should be available/done, it is also important describe what should not be done any more (if important)*
- *Focus on first line treatment*
- *General description/ characteristics of chemotherapeutic agents will be part of roadmap – describe in this tumour-type specific part the combinations used and dose modifications in case of adverse events, toxicities or allergic reactions*

INTRODUCTORY PAGE

Name of tumour entity

Craniopharyngioma

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Document version and date

Version 2, date 13-11-2021

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1. BACKGROUND AND RATIONALE

1.1 Background

Craniopharyngioma (CP) presumably derive from neoplastic transformation of ectodermal-derived epithelial cell remnants of the Rathke's pouch: an up growth from the roof of the stomodeum that forms the adenohypophysis. Adamantinomatous and papillary CPs are separate tumour types of epithelial origin with distinctive epidemiology, radiological features, histological, and molecular characteristics. Whereas papillary CP is principally a disease of adults (peak incidence: 30–59 years old), the large majority of CP occurring in paediatric age are adamantinomatous.

CPs are located either intrasellar or suprasellar. Although, CPs may develop at any point along the pituitary–hypothalamic axis, from the intrasellar region to the third ventricle of the brain, ~50% originate at the level of the third ventricle floor, within the infundibulum and/or tuber cinereum regions (including the vital hypothalamus), and predominantly expand to the third ventricle cavity [1]. CPs occur at any age, in children < 18 years of age they account for 5-11% of intracranial tumours [1, 2]. Paediatric patients with CP typically present with endocrine abnormalities, visual disturbances, and / or increased intracranial pressure [2]. The objectives of treatment in CPs are: (1) relief of raised intracranial pressure if necessary; (2) reverse visual compression symptoms; (3) restoration or substitution for pituitary hormone deficits plus all other supportive measures; (4) prevention of tumour regrowth/progression, while keeping acute and long-term morbidity and mortality as low as possible [3]. Neurosurgery with partial or total tumour resection, with or without radiotherapy, represents the current therapeutic standard of care [4-6]. The extent of neurosurgical resection has been a topic of debate, and the aim of Gross Total Resection (GTR) has been shifted to limited resection with or without radiotherapy [7-10]. Treatment strategy is based on visual symptom and/or degree of hypothalamic involvement seen on detailed Magnetic Resonance Imaging (MRI) [8, 11]. Neurosurgery is the first step in treatment of CP, after which observation or (delayed) radiotherapy are options. Highly conformal image guided adaptive radiotherapy approaches either by the use of photons or protons should be considered standard of care and can provide a safe and effective treatment option if indicated, in addition to a partial resection [12]. For target volumes < +/- 3 cm there seems to be no additional advantage for the use of photons. This combined treatment policy has shown to be effective in order to control CPs [13, 14]. Other treatment options may be considered, like intra-cystic treatment with interferon alpha [15, 16]. In case of predominant or mono-cystic CP, treatment with intra-cystic interferon alpha may create shrinkage of cyst volume with relieve of mass-effect on surrounding structures (optic pathways) while preserving the present pituitary function [17]. Although evidence is limited for this treatment option, a few reports show that treatment with intra-cystic interferon alpha is safe and may be beneficial as it can delay the need for surgery and/or radiotherapy. Last, also a wait and see may be an option, in case of a small asymptomatic intrasellar lesion [18].

CP has an excellent prognosis for tumour control, but the tumour and its treatment induce significant health and behavioural problems, mainly due to visual pathway involvement and hypothalamic damage (HD) [8, 19, 20]. The hypothalamic–pituitary location and tumour-related and/or treatment-related injury to these areas confer severe morbidity including blindness / low vision, hypothalamic obesity, panhypopituitarism, cognitive impairment, neurobehavioral abnormalities, and decreased life expectancy. To improve the prognosis of CP patients, a multidisciplinary setting in centralised hospitals with experienced

neurosurgeons and radiation oncologists and special expertise focusing on physical and psychosocial health is recommended. Further, the development of risk-adapted neurosurgical and radio-oncological treatment strategies are necessary to minimize hypothalamic damage [6, 18, 21].

2. PATIENT GROUP

CP account for 1.2-4.6% of all intracranial tumours, with a prevalence of 0.5-2.5 new cases per 1 million people per year worldwide [22-24]. In children, CP account for about 5-11% of all brain tumours, and of all CP's 30-50% is diagnosed during childhood and adolescence [22]. The peak incidence of CP's in children lays between the age of 5 and 15 years [24, 25]. There are two CP subtypes: adamantinomatous and papillary [26]. Mainly, the adamantinomatous CP (ACP) are seen in paediatric cases.

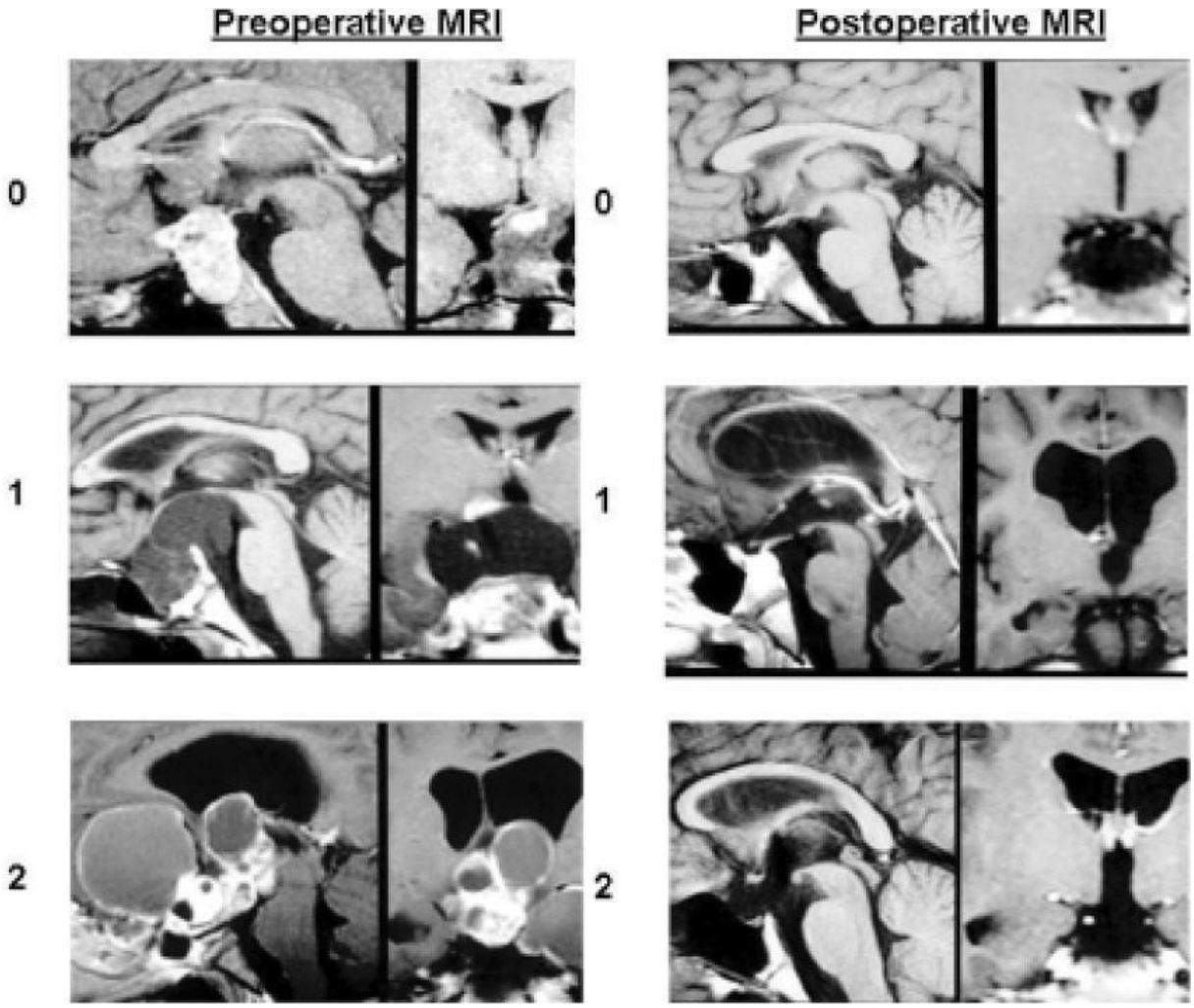
2.1 Diagnostic Criteria

Diagnosis of CP is obtained via magnetic resonance imaging (MRI) and tissue biopsy or analysis of cyst fluid.

2.1.1 Imaging

CPs occur in the supra sellar (75%), supra and infra sellar (20%) and infra sellar (5%) regions [27]. To reduce morbidity and mortality associated with surgery, an accurate preoperative assessment is important to estimate the exact tumour topography and the type of tumour adherence to the hypothalamus, optic chiasm, third ventricle, pituitary stalk and adjacent vessels [28-31]. Several pre and postoperative classification system are developed, such as Puget and the Muller grading, to grade hypothalamic involvement on MRI (figure 1) [8, 11].

Figure 1.



Preoperative *(left column)* and postoperative *(right column)* MR imaging classification of pediatric craniopharyngiomas. *Upper Left:* Grade 0, no hypothalamic involvement. *Center Left:* Grade 1, hypothalamus displaced by the tumor. *Lower Left:* Grade 2, hypothalamic involvement. *Upper Right:* Grade 0, no hypothalamic damage. *Center Right:* Grade 1, minimal hypothalamic damage. *Lower Right:* Grade 2, severe hypothalamic damage. [© Journal of Neurosurgery, 2007 [8]]

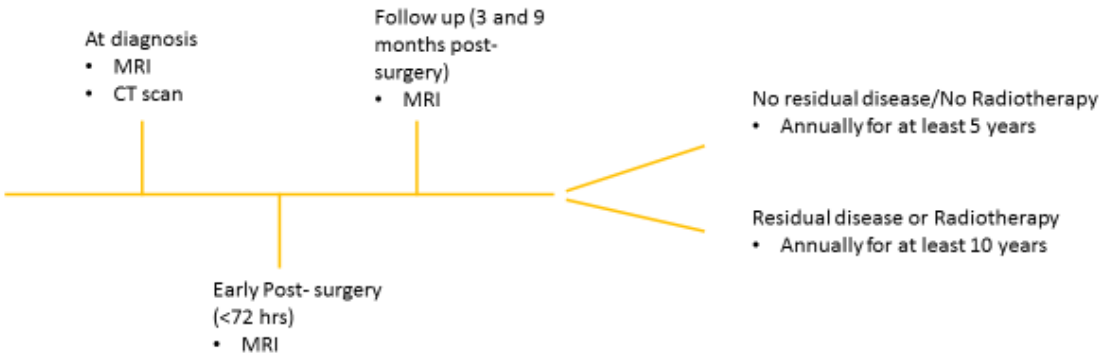
The imaging workup of CPs and the differential diagnosis from other sellar and suprasellar tumours is based on MRI with an adjuvant role of computerized tomography (CT) in the detection of calcifications [32]. Among tumours of this region, CPs are may be easily identified on preoperative imaging, but in all cases the differential diagnosis must be made of chiasmatic glioma, for which the identification of its relationship with optic nerve system can differentiate and germ cell tumours, which can be located in this area as well, for which tumour markers can be determined [33]. ACPs are predominantly cystic, show typically prominent calcifications and demonstrate contrast enhancement in the cyst walls ("90% rule"); PCPs are more frequently non-calcified and 'solid' [34]. An essential aspect of imaging in CPs is not only to visualize the characteristics and the delineation of the tumour but also to describe its relationship to the eloquent structures of the surrounding anatomy like the visual pathways, the pituitary stalk and the hypothalamus.

MRI is the imaging modality of choice in the assessment of CPs; high three-dimensional spatial accuracy and tissue-contrast definition are achieved by the combined use of 3D high-resolution axial, sagittal, and coronal T2-weighted images and volumetric T1-weighted sequences. The use of an intravenous contrast agent is strongly recommended for the evaluation of CPs at presentation. Advanced MRI modalities, such as diffusion-weighted imaging or MR spectroscopy, could be useful for the differential diagnosis and identification of recurrent disease. Magnetic resonance angiography (MRA) helps to differentiate a tumour from a possible vascular malformation and can be useful to depict the relationships between the tumour and specific arterial vessels [32].

Early postoperative MRI (within first 48-72) hours is recommended in order to assess the presence and extent of residual disease as well as possible surgery-related complications. During radiotherapy imaging surveillance is requested during radiotherapy, as cystic enlargement may occur and evacuation of the contents of the cyst till the target volume is mandatory.

Follow up with imaging is necessary to identify tumour recurrence of gross total or growth of partially resected CP, In children without any residual disease MRI follow-up is advised at least 5 years, in children with partially resected CP MRI follow-up is advised until 10 years after diagnosis. It must be noticed that rarely, secondary malignancy in radiotherapy-treated children may occur several years after the completion of treatment . Surveillance for such secondary malignancies may be considered after careful consideration of the potential harms and benefits of surveillance for CNS neoplasms [35]

Figure 2. CP imaging roadmap



2.1.2 Histopathology

ACPs present as a lobulated mass with solid, cystic and calcific components; cysts contain a mixture of cholesterol crystal, calcifications, and necrotic debris resembling machinery oil.

Adamantinomatous tumours may superficially infiltrate neighbouring brain and adhere to adjacent blood vessels and nerves. Key microscopical features of ACPs are sheets of squamous epithelial cells with peripheral palisading, wet keratin (which occasionally might be calcified) and stellate reticulum associated with surrounding gliosis and Rosenthal fibbers. The inflammatory cells associated with these tumours are mainly macrophages and T lymphocytes.

ACPs show aberrant nuclear accumulation of beta-catenin, especially in whorl-like epithelial cell clusters along the tumour margin and in finger-like tumour protrusions into the adjacent parenchyma [36].

PCPs are solid or rarely cystic encapsulated tumours, without cholesterol-rich machinery oil-like fluid or calcifications with cauliflower-like macroscopic morphology. The essential microscopic features of PCPs include well differentiated non-keratinizing squamous epithelium and papillary fibrovascular stroma [37]. PCPs frequently show immunohistochemical positivity for BRAF V600E mutation [38].

2.1.3 Molecular pathology

CTNNB1 mutation is the only consistent genomic alteration identified in ACP [39]. It occurs in as many as 95% of cases and determines aberrant nuclear expression of beta-catenin and canonical expression of WNT pathway target genes [40]. Several recent studies have detailed the key role of the inflammatory/immune response and of senescence in the pathogenesis of ACP. Senescence-associated secretory phenotype (SASP) harbours senescent cell clusters which are likely to act on surrounding epithelial tumour cells to promote proliferation, invasion and an overall protumorigenic microenvironment [41-48].

Recent insights into proteomics of paediatric brain tumours suggests that a subset of paediatric CP, despite their lack of BRAFV600E mutations, showed similar proteomics changes as those in BRAFV600E paediatric Low Grade Glioma tumours [49]. Specifically downstream proteins/substrates of MEK/ERK kinases, including ERK1/2, were upregulated in these samples. The PCP occurring in adults specifically harbour the BRAFV600E targetable mutation [50].

2.1.4 Clinical presentation and diagnostic work up

Children with CP may present with poor linear growth, late puberty, weight gain, visual deficits but also with symptoms due to intracranial pressure, such as headache or acute visual deterioration. In retrospect, the endocrine deficits, are often present far before the diagnosis. Most frequent hormonal deficiencies at presentation are growth hormone, thyroid-stimulating hormone (TSH), and gonadotropin deficiency [51-53]. Visual impairment commonly manifests as decreased visual acuity, visual field defects and/or abnormal pupillary responses; increased intracranial pressure can lead to papilledema with subsequent optic atrophy and permanent vision loss [54]. Timely detection of raised intracranial pressure and visual impairment is crucial as visual problems may be reversible in early stages of visual impairment if adequate treatment is provided: raised intracranial pressure and/or vision loss are indications for urgent surgical decompression [55]. Patients with no imminent threats should undergo personalized treatment after a multidisciplinary discussion. Before

emergency or planned surgery an anaesthesiological evaluation is recommended and cortisol, thyroxine or ADH deficiencies should be corrected (Figure 2) [56].

2.1.5 Differential diagnosis

The differential diagnosis of (supra)sellar masses include hypothalamic glioma and optic pathway glioma, germ cell tumours, Langerhans cell histiocytosis (LCH), Rathke's cleft cyst, xanthogranuloma, dermoid and epidermoid cysts, pituitary adenoma, granular cell tumour of the sellar region, pituicytoma, spindle cell oncocytoma, thrombosis of arachnoid cysts, colloidal cyst of the third ventricle, an aneurysm, and rare inflammatory variations [57, 58].

Table 1. CP diagnostic workflow

Evaluation	At diagnosis
Patient history	• Family history • Previous medical history • Timing of symptom onset • Neurological symptoms (headache, nausea, epileptic insults, motoric development, school performance) • Visual symptoms • Symptoms of hormonal deficiency (polyuria/polydipsia, short stature/obesity/delayed or precocious puberty/hypothyroidism/fatigue) • Fluid intake/urine output • Sleep issues/personality changes/school challenges • Changes in appetite • Activity schedule • Temperature-regulation problems
Physical examination	• General paediatric physical examination • Weight/height/body mass index (BMI) plotted on growth charts • Pubertal stage (Tanner) • Neurological examination
Ophthalmological	• Visual acuity • Visual fields • Optical nerves • Ocular motility
Chemistry	• Serum electrolytes • Serum and urine osmolality

	• Serum levels of alpha-fetoprotein, beta-HCG and prolactin • CSF levels of alpha-fetoprotein and beta-HCG (in selected cases)*
Endocrine	• Growth charts • Parental heights • Pubertal status (Tanner stage) • Evaluation of hypothalamic-pituitary axis (basal lab including IGF-1, TSH, FT4, LH/FSH, estradiol /testosterone, morning cortisol) • Endocrine stimulation tests may be considered (dependent on the individual situation; GH stimulation test, low dose synacthen / metyrapone testing).
Neurosurgical	• To determine timing of surgery based on threat to vision and /or high ICP • Determine options of limited surgery based on grading of hypothalamic involvement
Anaesthesiological	• Pre-operative screening
Psychosocial	• Support to patient and family from psychologist and social worker • Questionnaires
Neurocognitive	• Neurocognitive testing
Multidisciplinary discussion	• Strategy for therapy and to discuss conclusions from diagnostic work-up

* In doubt of GCT add spinal MRI and CSF cytology to estimate potential metastasis.

2.1.6 Genetic counselling

There is currently no known genetic relationship. There are, however, a few familial cases reported in the literature and a high proportion of the so-called “ectopic” CPs have been observed in individuals with Gardner syndrome caused by changes (mutations) in the *APC* gene (associated with beta-catenin) and inherited in an autosomal dominant manner, also causing polyposis coli. [59-62].

3. TREATMENT DETAILS

3.1 Treatment

3.1.1. Surgery

In case of increased intracranial pressure an endoscopic fenestration of the cystic lesion or an external ventricular drainage should be considered. For predominant mono-cystic tumours

intracystic therapy should be considered and intracystic catheter placement connected to a subcutaneous reservoir might be indicated.

Tumour resection, with or without radiotherapy, represents the current therapeutic standard of care [47]. Outcomes of neurosurgery of a childhood brain tumour have been related to the specific experience of the neurosurgeon [63], for this reason it is encouraged to centralize this care in high volume centres with experienced neurosurgeons embedded within a multidisciplinary team, if feasible [64].

The best option for treatment depends on the tumour characteristics such as cystic and solid components and the relation of the tumour to the adjacent important structures, such as the optic nerves and pituitary-hypothalamic region [65, 66]. Hypothalamic involvement can be graded using either the Paris or the Muller grading [8, 11]. A major factor that affects children with CP is hypothalamic dysfunction with associated obesity [20, 47]. In the paediatric population, preoperative hypothalamic involvement (especially Paris grade 2, see figure 1) increases the risk of preoperative and postoperative obesity, and subsequently hypothalamic damage during surgery increases the risk of postoperative weight gain [67, 68]. Therefore, complete resection is only recommended when there is no hypothalamic involvement present (Paris grade 0). Neurovascular injury and (additional) visual impairment should always be prevented [69, 70]. A pre-operative strategy concerning the feasibility of a safe extent of resection contributes to avoidance of additional hypothalamic damage in combination with relieve of visual symptoms. The neurosurgical approach to the tumour depends on the location and the configuration of the lesion. The transsphenoidal approach should be considered in case of a sellar location either with a clear view on the suprasellar extension. The transcranial approach has several options, pterional, subfrontal or transcallosal, and is primarily determined by the configuration of the lesion and the preference of the experienced neurosurgeon.

As CPs are rare and anatomical involvement and/or surgical lesions of posterior hypothalamic areas can result in serious quality of life-compromising sequelae, such as hypothalamic obesity, psychopathological symptoms, and/or cognitive problems. Timely discussion of the most appropriate and feasible treatment option per patient should be held preferably in a multidisciplinary setting including an experienced neurosurgeon, oncologist, radiotherapist, radiologist, endocrinologist and ophthalmologist should always be pursued [5, 6, 20, 47, 71].

The postoperative after care should be guaranteed on ICU with strict sodium controls and fluid balances since diabetes insipidus and could occur within 72 hours requiring secure monitoring [72].

3.1.2 Radiotherapy

Since complete resection of CP is often not intended due to hypothalamic involvement, radiotherapy has an important role in the treatment of CP [47]. Depending on age, tumour location and extent, and pituitary function the timing of radiotherapy can be chosen shortly after limited surgery or to be delayed to till progression is evident[13]. These options should be considered in a multidisciplinary discussion on a case-by-case basis, taking the amount of residual disease as well as potentially endocrine, cognitive, and vascular morbidity of radiation into account [73]. Once the indication for radiotherapy has been established, treatment preparation includes a head mask, and a CT-scan in treatment position with accurate co-registration of a recent MRI-scan. While the Clinical Target Volume (CTV)

margin (1 to 5 mm) is still a matter of debate, the Planning Target Volume margin can be reduced to 1 mm when all criteria for modern image-guided radiotherapy are fulfilled. A total dose of 54.0 Gy in 30 daily fractions of 1.8 Gy, using image-guided adaptive radiotherapy with daily online position corrections should be considered as gold standard. In patients with CP and cystic components (weekly) repeated imaging with target volume adaptation is recommended [74]. Depending on target volume size and extension, a benefit of proton therapy can be expected in a subgroup of patients. Some studies have shown that mortality and morbidity may be decreased over time due to the treatment shift of gross total resection to partial surgery with irradiation [7, 75, 76]. However, long term studies with large enough cohorts and follow-up time are needed to confirm these results.

3.1.3 Targeted therapy

3.1.4 Intracystic therapies

Intracystic therapy can be considered in selected patients in case of large and / or mono-cystic lesions with the aim of volume reduction and maintaining (partial) pituitary function delaying further progression and also delaying more invasive treatments [17]. There are multiple cystic therapies, but interferon-alpha appears to have an improved toxicity profile compared with earlier intracystic therapies, including bleomycin and radioisotopes [15, 77]. Intracystic therapy three times a week can be administered via a reservoir with an indwelling catheter, situated in the cystic lesion. The effect of interferon is thought to be caused by an anti-proliferative and immunomodulatory pathway, inducing apoptosis [77]. However effectiveness is to be judged on MRI on individual basis since conclusions on the efficacy of this therapy remain uncertain. Analysed cohorts were retrospective and limited in size and circumstances, while the reported outcomes after therapy vary between studies [15, 77, 78]. In the largest internationally gathered group of 56 patients, treatment delay of median 5.8 years [1.8–9.7] was reached in 42 out of 56 patients with a median age of 6.3 years [0.3–17] at diagnosis [17].

3.1.5 Upcoming treatments

Due to insights of the pathology of CP new targeted therapies are arising. ACPs have been found to have an inflammatory nature, which suggests that novel therapies aiming to inhibit cytokine signalling may be of relevance. IL-6 or IL-1 inhibitors are already available in children for other indications such auto-immune diseases. A recent study showed promising results in treating cystic ACP by systemic administration of tocilizumab as IL-6 inhibitor [79]. Additionally, the use of PD-1 inhibitors may be of relevance in ACP and require further attention in preclinical evaluation [80].

Another pathway of interest for targeting is the MAPK/ERK pathway; recent studies found that inhibition of the MAPK pathway using trametinib, a specific MEK inhibitor, reduces the proliferative index and increases apoptosis of tumour cells in explant cultures of both mouse and human ACP [81, 82]. The MAPK/ERK pathway may therefore be a novel therapeutic target as well, which needs to be further explored. With regards to the papillary subtype of CP, the identification of the BRAF mutation, raise interest to study targeted therapy with BRAF and MEK inhibitors. A US national phase II trial (ClinicalTrials.gov NCT03224767) is currently ongoing for analysis of the safety, tolerability and pharmacokinetics of vemurafenib and cobimetinib in patients with BRAFV600 mutated PCP.

Therapy

- **In case of hydrocephalus and / or endangered vision:**
  - Emergency surgery to relieve pressure
    - direct surgical approach or
    - aspirate cyst fluid with or without placing an intracystic catheter in case of a cystic lesion

- **Discuss in multidisciplinary setting the best treatment for the patient at diagnosis and at relapse depending on the results of the diagnostics.**
  - Wait and scan (small asymptomatic intrasellar lesion)
  - Gross total resection (intrasellar lesions without hypothalamic involvement)
  - Partial resection with/without adjuvant radiotherapy
  - (Adjuvant) radiotherapy
  - Intracystic therapy

4. LONG TERM OUTCOME

CP survivors experience increased morbidity and decreased QoL which is related to the degree of hypothalamic dysfunction, overweight, visual dysfunction and neuro-psychological situation. To provide high quality care for this complex patient group, centralization of care and follow-up of children with CPs in specialist centres is needed, with presence of a multidisciplinary team experienced in treating these tumours during childhood. This team should at least include a paediatric endocrinologist, oncologist, neuro (pituitary) surgeon, neurologist, physiotherapist, dietician, rehabilitation doctor, psychologist, and ophthalmologist.

4.1.1 Pituitary outcome

Pituitary dysfunction is one of the most frequent sequelae in patients with CP [83]. Forty to ninety percent of children with CP already have one or more pituitary disorders at the time of diagnosis [84]. Depending on the anatomical location of the CP and hypothalamic involvement, the rate of pituitary disorders increases [7, 85]. Growth hormone deficiency is the most common anterior pituitary deficiency, with prevalence reported up to 88-100% of the patients [86, 87], gonadotropin deficiency in 80-95% of the patients, TSH deficiency in 39-95% and postoperative adrenocorticotropic hormone (ACTH) deficiency occurs in 55-88% of the patients [47]. Diabetes insipidus is observed preoperatively in 17-27% of all CP patients, with transient post-surgical DI up to 80-100% of the patients [52, 84, 88]. Permanent DI is found in between 40-93% [73]. These endocrine deficiencies require lifelong hormonal substitution [89].

4.1.2 Hypothalamic outcome

Damage, due to the tumour or its treatment, to the important nuclei of the hypothalamus, such as the ventromedial hypothalamus (VMH), the arcuate nucleus (AN), and the paraventricular nucleus (PVN) prevents integration of peripheral hormones, such as ghrelin,

leptin, and insulin and therefore causes food craving and decreases caloric expenditure [19]. Hypothalamic dysfunction (HD) may lead to obesity, psychosocial disorders (obsessive compulsive disorders), adipsia, autonomic regulation disturbances as temperature dysregulation, low heart rate variability and sleep disturbances [90]. HD is found at diagnosis in at least 35% of childhood-onset CP patients. After treatment, the prevalence of hypothalamic dysfunction increases drastically, with prevalence reported up to even 65–80% in some studies [91].

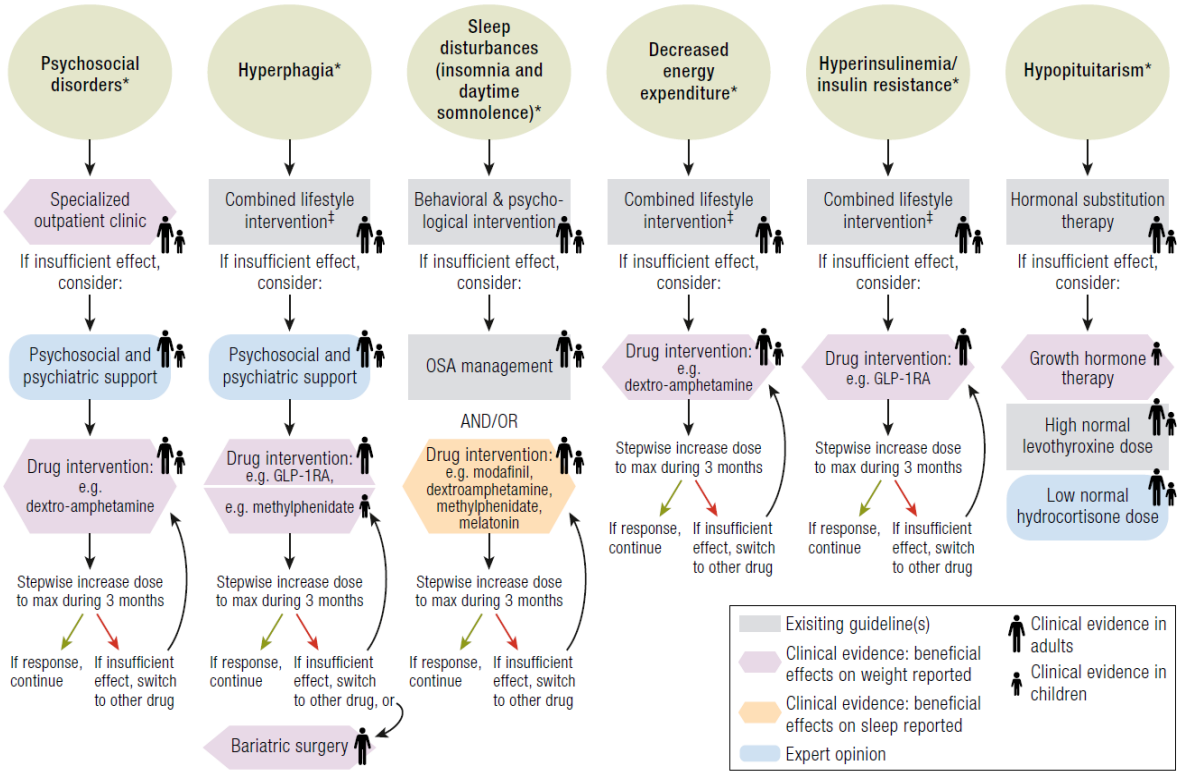
Weight gain occurs mostly in the first 6-12 months after surgical treatment, but is also seen after hypothalamic radiation [85, 92]. Most important in the prevention of HO is to minimize hypothalamic damage caused by treatment. Neurosurgical caution is therefore very important to preserve hypothalamic integrity. The clinical, neuro radiological, and surgical definition of hypothalamic involvement is a fundamental factor related to poor postoperative outcome and progressive obesity in children after neurosurgical removal of CP [14, 19, 68, 93].

HD may result in progressive weight gain, however differences within patients are seen dependent on the degree of HD [68]. Hypothalamic obesity not only reduces patient quality of life, it also increases risk of metabolic disease, with risk for multiple morbidities and premature mortality [20, 23, 47, 94].

Hypothalamic obesity is often unresponsive to conventional treatment efforts such as lifestyle modifications and may, therefore, require pharmacological intervention [95]. None of the current approaches however have been proven to be effective for patients with childhood-onset ACP and hypothalamic obesity [47, 67, 71, 96]. An individualized stepwise treatment algorithm has been proposed by van Iersel et al., which may be used to approach the patient with HD following treatment for CP (Figure 2).

Figure 3. Individualized stepwise treatment algorithm for hypothalamic obesity
The complexity of factors led to the following algorithm approach. The first step is to identify clinical symptoms of the patient in the six domains (i.e., psychosocial disorders, hyperphagia, sleep disturbances, decreased energy expenditure, hyperinsulinemia/insulin resistance, and hypopituitarism). In many patients with CP or suprasellar tumours, symptoms within different clinical domains are present simultaneously. Recommended initial interventions are located below each clinical domain in the treatment algorithm. If the effect of the intervention is insufficient, the next step in the algorithm should be pursued. For drug interventions, a stepwise increase in dose up to the maximum tolerated dose is recommended for the first 3 months. All interventions are categorized as clinical evidence (hexagons), existing guidelines (rectangles), or expert opinion (rectangles, round).

‡Combined lifestyle intervention includes dietary, physical activity, and behavioural support. GLP1-RA, GLP-1 receptor agonist. [© 2019 Illustration Presentation ENDOCRINE SOCIETY]



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4.1.3 Visual outcome

Visual disturbances are common in childhood CP patients, due to pressure of the tumour to the optic chiasm. In more than 50% of patients, visual acuity and visual field impairments are present at time of diagnosis, and in 13.8% blindness in one or two eyes [54]. Post-surgically recovery of visual deficits has been described in several cohorts varying between 33 - 47 % [84, 88, 97].

4.1.4 Neuropsychological and social outcome

QoL in CP patients is influenced by tumour progression or recurrence, hypothalamic involvement, BMI, hydrocephalus, and age of onset but can also be hampered by visual function and lack of energy [98, 99]. The psychosocial and emotional domain tends to affect the QOL the most, which is deprived in about 50 % of patients [100]. Social impairment, especially social withdrawal and internalizing behaviour, has been described to be present in 35% of all CP patients [100]. Only 10-25% of CP patients end up in a marriage-like relationship [101]. Also, psychopathological symptoms such as anxiety, depression, withdrawal and apathy are frequent in long term survivors of childhood CP [102]. Younger age at diagnosis and pre-surgical functional impairments are known risk factors associated with reduced psychosocial and neurocognitive function after treatment [83, 93, 103]. Of all, hypothalamic dysfunction is the most clinically relevant negative risk factor for impairments in social functioning and self-image [102]. As in other types of acquired brain injury (ABI) children with CP encounter neurocognitive sequelae mostly including problems with attention, working memory, and executive function [102, 104, 105]. Sleep disorders, including excessive daytime sleepiness, are also a significant cause of morbidity in patients with CP and correlate with decreased quality of life [106]. Combined lifestyle interventions as indicated for hypothalamic dysfunction can also be supportive for cognitive functioning. The long term consequences of CP are also relevant in the perspective of daily family life and attention for parents and siblings is advocated [107, 108].

Follow-up*

- **Tumour follow-up (MRI)**
- **Endocrine follow-up and treatment by paediatric endocrinologist**
- **Weight management (combined life style intervention low caloric intake including dietician & physiotherapist for daily physical activity, monitoring of body composition)**
- **Neuro-psychological and social: support by psychology and social work, coaching and monitoring of school performance, family life and diagnostic neuro-cognitive testing in the perspective of ABI**
- **Ophthalmological follow-up and coaching of visual impairment in daily life if indicated**
- **Rehabilitation for management of fatigue/energy, sleep adequate with occupational therapy on indication**
- **Neurological follow-up if indicated**

* Follow-up should be done by a multidisciplinary team experienced in treating children these tumours during childhood. This team should at least include a paediatric oncologist, neuro (pituitary) surgeon, paediatric endocrinologist, physiotherapist, dietician, child psychologist, social worker, ophthalmologist, rehabilitation doctor, and neurologist

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