Novel perspectives in diagnostics, treatment and follow-up of childhood-onset craniopharyngioma

Hermann L. Müller[1], Thomas E. Merchant[2], Stephanie Puget[3], Juan-Pedro Martinez-Barbera[4]

[1]Department of Pediatrics, Klinikum Oldenburg AöR, Medical Campus University Oldenburg, 26133 Oldenburg, Germany; [2]Division of Radiation Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee, USA; [3]Service de Neurochirurgie, Hôpital Necker-Enfants Malades, Sorbonne Paris Cité, Paris, France; [4]Developmental Biology and Cancer Programme, Birth Defects Research Centre, UCL Great Ormond Street Institute of Child Health, University College London, London, UK

Corresponding author and person to whom reprint requests should be addressed:

Hermann L. Müller, M.D.

Department of Pediatrics, Klinikum Oldenburg AöR, Medical Campus University Oldenburg

Rahel-Straus-Strasse 10, 26133 Oldenburg, Germany

Phone: ++49-441-4032013; Fax: ++49-441-4032887

e-mail: mueller.hermann@klinikum-oldenburg.de

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Abstract

Childhood-onset craniopharyngiomas are rare embryonal malformations of low-grade histological malignancy. Novel insights in molecular pathogenesis of human adamantinomatous craniopharyngioma has started to be unveiled offering the possibility of testing novel treatments targeting pathogenic pathways. Hypothalamic involvement and/or treatment-related lesions result in impaired physical and social functionality and severe neuroendocrine sequelae. Quality of survival in craniopharyngioma with hypothalamic involvement is impaired by severe obesity, physical fatigue, and non-optimal psychosocial development. Patients with craniopharyngioma involving hypothalamic structures show reduced 20-years overall survival, whereas overall and progression-free survival rates are not related to the degree of surgical resection. Irradiation is effective in prevention of tumor progression and recurrence. For favorably localized craniopharyngiomas, the preferred treatment of choice is an attempt at complete resection with preservation of visual, hypothalamic, and pituitary function. For unfavorably localized tumors with close proximity to optical and/or hypothalamic structures a radical neurosurgical strategy attempting complete resection is not recommended in order to prevent severe sequelae. As expertise has been shown to have impact on post-treatment morbidity, medical societies should establish criteria of adequate professional expertise for the treatment of craniopharyngioma. Based on these criteria, health authorities should organize the certification of centers of excellence authorized for treatment and care of patients with this chronic disease.

Key words: craniopharyngiomas, hypothalamus, irradiation, neurosurgery, obesity, quality of life.

Introduction

For decades gross-total resection was the preferred treatment option in childhood-onset craniopharyngioma (CP), assuming that radical strategies at the time of initial diagnosis and treatment would result in the cure of CP.

Recent reports on long-term prognosis, novel neurosurgical and radiooncological treatment approaches, and molecular genetics provide new insight into more risk-adapted treatment in CP in order to prevent severe sequelae such as hypothalamic syndrome and obesity[1-4].

Epidemiology

CPs are rare, with an incidence of 0.5 to 2 cases per million persons per year [5]. A bimodal age distribution has been shown, with peak incidence rates in children of ages 5 to 14 years and adults of ages 50 to 74 years [6, 7].

Clinical presentation and diagnostics

The diagnosis of childhood-onset CP is often made late [8] — sometimes years after initial appearance of symptoms — with a clinical picture often dominated by manifestations of intracranial pressure Further primary manifestations are endocrine deficits (52–87%) and visual impairment (62–84%). Hormonal deficits are frequently caused by disturbances to the hypothalamic–pituitary axes that affect growth hormone secretion (75%), gonadotropins (40%), thyroid-stimulating hormone (TSH) (25%), and adrenocorticotropic hormone (ACTH) (25%) [9].

In a study of Hoffmann et al.[10], median duration of history was 6 mo (range: 0.1–108 mo) and correlated positively with age at diagnosis. Tumour size, hypothalamic involvement, degree of resection, and BMI at diagnosis were not related to duration of history. In multivariate analysis adjusted for age at diagnosis, only hydrocephalus was found to have a significant influence on duration of history. Visual and neurological deficits were associated with larger initial tumour size and impaired 10-yr OS. Weight gain and growth failure were observed

with longest duration of history. PFS and functional capacity were not related to any specific symptom. Endocrine deficits at diagnosis were associated with long duration of history[10].

With regards to the anatomical landmarks of help to achieve a precise preoperative MRI diagnosis of the accurate topographical relationships between the tumor and the hypothalamus/optic chiasm/third ventricle some studies have identified important signs to be considered [11, 12]. The solid mammillary bodies are grossly displaced/distorted by the lesions involving the hypothalamus but do not become invaded by the tumor as a rule. The position and distortion of the mammillary bodies can be identified preoperatively and helps to predict the relative position and adherence of the distorted hypothalamus [13]. The use of heavily T2-weighted MR [14] and FIESTA MRI sequences [15] allow an optimal identification of the brain-CP interphase as well as the relative position of the hypothalamus both essential for the planning of surgical/radiotherapy treatments.

Molecular pathology of adamantinomatous CP

It is now well established that the vast majority, very likely all, of the human adamantinomatous CP tumours carry over-activating mutations in the gene encoding beta-catenin (*CTNNB1*) [16-19]. Of note, the papillary form of CP, which usually present in the elderly, carry *BRAF p.V600E* mutations and show distinct methylation profiles, indicating that adamantinomatous CP and papillary CP have two different molecular identities [19, 20]. Recently, the coexistence of *BRAF p.V600E* and *CTNNB1* mutations have been reported in one case of adamantinomatous CP [21]. Further molecular analyses are required to identify which, if any, other recurrent mutations are present in human adamantinomatous CP in addition to those in CTNNB1. Nonetheless, it seems likely that human adamantinomatous CP is a tumour with a low mutation burden.

Most of the identified mutations in adamantinomatous CP lie in regulatory amino aids encoded by exon 3 of the *CTNNB1* gene [22]. The molecular consequence of such mutations is the expression of a mutant form of beta-catenin with increased degradation resistance,

resulting in the accumulation of beta-catenin and subsequent activation of the WNT pathway. Confirming this, human adamantinomatous CP contains cells with nucleo-cytoplasmic accumulation of beta-catenin, which are either dispersed throughout the tumours or grouped in whorls of cells, termed cell clusters [23-25]. These clusters are not present in any other pituitary tumour and represent a histological hallmark of human adamantinomatous CP [26]. Tumour cells including cell clusters, activate the WNT pathway, as evidenced by the expression of gene targets such as *AXIN2* or *LEF1* [23, 24].

Gene expression profiling studies of human adamantinomatous CP have been performed to better characterize its pathogenesis downstream of the activation of the WNT/beta-catenin signaling [20, 27]. These studies have revealed several pathways that are deregulated in these tumours as a consequence of the over-activation of the WNT/beta-catenin pathway (**Figure 1**). Many of the deregulated pathways are targetable with specific inhibitors, which could potentially offer new therapeutic opportunities. The next logical step is to perform well-designed pre-clinical studies to determine the function of these pathways in the biology of adamantinomatous CP. These pre-clinical studies will inform whether a particular pathway has anti- or pro-tumorigenic effects, and therefore, whether therapies should either aim to inhibit or promote its activity. This knowledge of adamantinomatous CP biology should facilitate the generation of human clinical trials specifically designed to assess the efficacy of particular drugs against human adamantinomatous CP. In our view, robust pre-clinical data is imperative before translating findings into the clinic, as some of the deregulated pathways may have functions that are tumour context dependent, and therefore, their therapeutic value needs to be assessed specifically in each tumour. Nonetheless, as in any targeted therapy, drug resistance may arise, although the low mutational burden of adamantinomatous CP tumours may be prevent the acquisition of such resistances.

Pre-clinical models of human adamantinomatous CP

There have been several attempts to establish pre-clinical models of human ACP, from primary cell cultures to genetically engineered mouse models (GEMMs) and patient-derived xenografts (PDXs).

Primary cells from human adamantinomatous CP samples have been isolated and used for diverse studies to assess the effects of the WNT/beta-catenin, Claudin-1 and EGF pathways in migration and invasion [28-30]. Although these experiments are encouraging and informative, no molecular profiling of these tumour cells has been carried out. In addition, these cells cannot be easily cultured and passaged. Further characterization of these cells (e.g. the degree of molecular similarity to the human tumours) and optimization of the culture conditions are required to achieve the maximum potential of this *in vitro* cell model.

A genetically engineered mouse model (GEMM) has been generated by expressing a mutant form of beta-catenin that is resistant to degradation in undifferentiated embryonic precursors of the pituitary gland (i.e. the embryonic adamantinomatous CP mouse model) [23]. Interestingly, when oncogenic beta-catenin is expressed in committed progenitors (e.g. *Pit1*-expressing cells) or hormone-producing cells (e.g. somatotrophs), no tumours develop, suggesting that only undifferentiated progenitors provide the cellular context required for tumours to form. This oncogenic beta-catenin is functionally equivalent to that identified in human adamantinomatous CP, therefore the molecular aetiology in this GEMM is similar to human adamantinomatous CP.

Several histological and molecular features are conserved between the mouse and human tumours. As observed in humans, mouse tumours show cystic and solid components, are synaptophysin-negative and do not express hormones. The pituitary gland of these mice at birth and early postnatal stages show the presence of clusters with nucleo-cytoplasmic accumulation of beta-catenin, which typifies human adamantinomatous CP. However, murine tumours do not show a clear palisading epithelium, wet keratin or any sign of calcification, all

common features in human tumours. Likewise, tumours do not infiltrate the brain or visual pathways in the mouse, but this is a common finding in humans. Despite the histological differences, molecular analyses of the mouse tumours have predicted the up-regulation of several gene pathways in the human, which have been later confirmed in human studies (e.g. SHH and C-X-C motif chemokine receptor 4, CCR4) [31-33]. Therefore, this model shows similar molecular aetiology and pathogenesis to human adamantinomatous CP, but there are species-specific differences that need to be considered [34].

A second GEMM has been obtained by targeting the expression of oncogenic beta-catenin into adult SOX2-positive pituitary stem cells (i.e. the inducible mouse adamantinomatous CP model) [35]. The resulting tumours also show a degree of resemblance with human adamantinomatous CP; specifically, these murine tumours are non-secreting and have beta-catenin-accumulating cell clusters. However, as in the embryonic model, these tumours lack some common histological features of the human tumours (e.g. palisading epithelium and wet keratin) and do not infiltrate the brain or visual pathways.

Importantly, these GEMMs have revealed that paracrine activity of mutated progenitors/stem cells may be critical in controlling growth and behavior of adamantinomatous CP, a concept that could have further implications in the cancer field [36]. Specifically, Sox2-positive pituitary stem cells have been targeted to express oncogenic beta-catenin simultaneously with a fluorescent reporter that allows genetic tracing of the descendants of targeted Sox2 cells. These experiments have revealed that the murine tumours are not derived from the targeted Sox2-positve cells, instead, these mutant Sox2-positive cells proliferate transiently whilst accumulating beta-catenin, then stop dividing but persist, generating the beta-catenin-accumulating cell clusters. Since the mutated cells stop proliferating it is important to ask: how do the tumours form? Molecular profiling of the murine clusters has demonstrated the expression of a plethora of signaling molecules including proliferative and survival signals as well as inflammatory cytokines and chemokines, which are hypothesized to generate a pro-

tumorigenic microenvironment that results in transformation of a neighboring cell (**Figure 2**). This paracrine model has been shown to be relevant in other murine neoplasia such as hepatocellular carcinoma and leukaemia [36, 37].

PDXs have also been developed, by transplanting pieces of biopsies from human adamantinomatous CP either subcutaneously [38, 39] or intracranially [40] into immunosuppressed mice. In these models, the cellular architecture of the original tumour is maintained, therefore offering a suitable model to test the effects of potential therapies and understand further the biology of these neoplasias. Using the intracranial model, it has been proposed that the paracrine activities of the clusters may be critical in controlling the infiltrative behavior of human adamantinomatous CP [40], a finding that is compatible with the 3D structure of human adamantinomatous CP recently reported [41]. These are certainly very promising tools, but have also some limitations. For instance, the tumours develop in an immunosuppressed environment, when inflammation is likely to play a critical role in the pathogenesis of these neoplasias [27, 31, 42, 43]. In addition, the rareness of human adamantinomatous CP makes it challenging to obtain biopsies and the slow growth of the engrafted tumours may make any analysis more difficult (**Table 1**).

In conclusion, there are several available pre-clinical models for human adamantinomatous CP, each of them accompanied by advantages and disadvantages. We anticipate that the combined use of some or all of these models may be required to assess the pathogenicity of particular pathways and the potential therapeutic efficacy of selective drugs.

Surgery

The surgical management of CP in children remains one of the more controversial topics in pediatric neurosurgery. Theoretically, the benign histology implies that total surgical excision should be sufficient to provide a cure.

In the past: Large pediatric surgical series showed their surgical success in radically resecting CPs [44-49]. However, the associated mortality (up to 50% at 10 years) and high rate of recurrence despite surgical clearance (up to 50% in some series) became apparent and it has been widely established, that in certain cases total excision may lead to unacceptable hypothalamic injury [50-53].

Present : The state-of-the-art in the surgical management of CP is now turning to multi-modality treatment strategies (combination surgery and radiotherapy) aiming to limit morbidity. In the beginning of the 2000's, the Necker's neurosurgical team proposed that the treatment strategy may be adapted according to the degree of hypothalamic involvement as shown by the pre-operative MRI [53, 54]. Recent technical advances such as neuronavigation, endoscopy (combined with microscpic resection for transcranial approaches or solely for endonasal transsphenoidal approaches) and per-operative imaging may help the neurosurgeon to safely remove the CP, preserving the hypothalamus structures.

Primary CP management is tailored to presentation.

In emergency: In some cases with recent signs of raised intracranial pressure (ICP) and/or visual loss, surgical decompression in emergency is required. In those cases, the clinical signs are mainly linked to hydrocephalus due to a CP cyst developed in the third ventricle impairing the CSF pathways. A ventriculoperitoneal shunt should be avoided (risk of dysfunction and hyperdrainage that can prevent a further safe transcallosal approach) and it is recommended to decompress the cyst by placement of a catheter and eventually an ommaya reservoir to allow repeated aspiration. The catheter can be placed during an open surgery (rare), a stereotactic procedure of preferably an endoscopic approach. Importantly, the decompression of a cyst may help in refining the risk grade [55].

For cystic CP, intracystic therapies can be performing after permeability test done one to two weeks after the initial surgery (injection of contrast medium in the subcutaneous reservoir). Radiotherapy agents (Yttrium-90 and Phosphorus-32) or chemotherapy with bleomycin has had some success but has been associated with neurotoxicity or even death and has not proven

to be consistently efficacious [56]. The most effective intracystic treatment with best benefit risk ratio seems to be obtained with interferon alpha. However, like for other intracystic therapies, the effect is limited to the cystic portion with no effect on the solid component and there is no available data published so far on the PFS after this treatment [56, 57].

Surgery based on the hypothalamus involvement: The neurosurgeon will therefore plan surgery(ies) according to (1) the goal for a total resection or according to the hypothalamus involvement (risk grading 0,1,2) (2) location of the tumor and identification of some anatomical landmarks to choose the best pathway(s). The anatomical landmarks important to identify before surgery are the length of the optic nerve pathways and the location of the anterior communicant artery, the sellar diaphragm, the hypothalamic structures (the mammillary bodies and the shape of the third ventricle floor), the size of the ventricles and the presence of a septum pellucidum.

- Grade 0: no hypothalamus involvement: most of these cases are developed in the sellar region, under the sellar diaphragm. An endoscopic endonasal transsphenoidal route is ideal in these cases and has been uncommonly used in pediatric CP due to their rarity compared to adults but also to unfavorable anatomic conditions such as small nostrils, non-pneumatized sphenoid sinus or short intercarotid distance [58]. However, in experienced teams, young patients' age does not seem to be an obstacle and more and more publications report the success of this technique [59-61]. Some authors claimed to avoid hypothalamic dysfunction with endoscopic endonasal transsphenoidal approach [62, 63] although it must be emphasized that the majority of tumors approached via this route are infra diaphragmatic in location [64].

- Grade 1: the CP is in contact with the hypothalamus that is pushed or compressed, this latter being still identified on pre-op MRI. In some cases, according to neurosurgeon's skills and the extension of the CP, an endoscopic endonasal transsphenoidal approach can be perform or a transcranial route, which has been traditionally used.

- Grade 2: the hypothalamus is invaded by the CP and cannot be easily identified. The most frequent transcranial routes are transcallosal, pterional and uni or bilateral subfrontal approaches. Different approaches can be done in the same patients in case of planned staged

surgeries to preserve hypothalamic structures. In case of lower displacement of hypothalamic structures, a transcallosal or a lamina terminalis approach should be preferred. On the contrary, an upper displacement of these structures should lead to a pterional or subfrontal approach. As the goal in these CP group is to preserve the invaded hypothalamus, the endoscopic endonasal transsphenoidal route is not recommended in these children as it may be difficult, through this approach by endoscope, to anticipate the localization of the remaining hypothalamus and the perforating arteries.

In fact, many CPs originate primarily within the infundibulum and/or the tuber cinereum and expands within the hypothalamus itself, representing the subpopulation which associate the highest adherence, highest recurrence rate and worst outcome [65]. Several papers demonstrate support the need of a hypothalamus-referenced classification of CPs [66-69]. About 40% of CPs in the different series present a predominant involvement of the hypothalamus [70, 71].

Pediatric CP rare lesions and their surgical treatment is very challenging, thus should be done in experienced centers. In case of grade 2 hypothalamic involvement, we recommend to decrease the tumor size as much as possible before irradiation, with combined surgeries if necessary. For children and especially the youngest with isolated endocrine deficits and without visual impairment or signs of raised ICP, a close follow-up with MRI should be discussed, to gain time and postpone the time for irradiation (in case of hypothalamus involvement).

Radiation therapy

Radiation therapy is an effective means to achieve long-term disease control in children diagnosed with CP. Advances in radiation therapy including highly-focused methods of intensity-modulated photon and proton therapy have been used with more generalized target volume reduction strategies to improve the therapeutic ratio and increase the margin of safety [72]. Understanding that these patients present with significant co-morbidities and are subject to sometimes unavoidable effects of tumor and surgery prior to irradiation helps to balance

treatment recommendations and accept irradiation as a primary treatment modality with proper attribution of long-term effects.

CP may be irradiated after neuroimaging diagnosis and without surgical intervention. Although these cases are uncommon, they comprise a unique group of patients that may be followed for radiation-related complications absent the contributions of other treatments. There are an increasing proportion of children treated with transnasal / transspenoidal surgery with goals similar to transcranial surgery - to decompress the tumor and improve or avoid symptoms – including attempted gross-total resection. The advantage of the transnasal approach has yet to be demonstrated in children who require irradiation; however, less invasive approach will create a new cohort of children to evaluate for outcomes and acute and late effects of treatment. Practical and early observations are concerns about the use of the transnasal approach in children with extensive and cystic tumors where unresected tumor may be prone to pseudotumor and cystic expansion during irradiation and necessitate transcranial intervention. That diabetes insipidus is generally accepted after transnasal surgery and might be avoided by transcranial approach is another consideration. Teams that lean toward less invasive surgery, so called “limited surgery” and radiation therapy consider the use of surgery (resection or catheter placement) to alleviate symptoms such as vision loss or other obvious neurological deficits, establish a diagnosis in the setting of equivocal neuroimaging assessment, and prevent symptoms when further progression might impact optic pathways, result in hydrocephalus, or compress neurological tissues such as the brainstem and increase the risks associated with irradiation. Indeed, surgery may be used to decrease the risks of irradiation when resection reduces the targeted volume, increases the distance between target and critical normal tissue structure or reduces mass effect, which might compromise tissues and increase the risk of severe complications including necrosis and vasculopathy.

Target volumes for radiation therapy are best delineated by multiplanar, multisequence MR imaging. CT is required for radiation dose calculation and plays a vital role in the treatment planning process for the assurance that it provides when the calcified tumor is included in the targeted volume. The borders between tumor and normal tissue are usually distinct when not

interrupted by surgery including borders where invasion or attachment may be present or boundaries where invasion or attachment may be unlikely.

In radiation oncology the gross tumor volume is defined as the residual tumor. In pediatric neuro-radiotherapy including the treatment of CP the gross tumor volume is often defined as the gross residual tumor and/or the tumor bed. When surgery is performed and portions of the tumor are resected or the borders of the tumor interrupted, the definition of the gross tumor volume relies on the post-operative imaging findings, a conversation between the surgeon and radiation oncologist, and experience and judgment of the radiation oncologist considering the advantages and disadvantages of limiting the extent of the targeted volume. Classic parallel-opposed portals defined on planar x-ray imaging gave way to CT-based treatment planning more than 20 years ago. And while the earliest experience with conformal treatment planning irradiated relatively large margins of normal tissue surrounding the post-operative tumor complex, the move toward image-based treatment planning substantially reduced the amount of normal brain collaterally irradiated defining a new cohort of children for the evaluation of disease control and treatment related complications. The distinction between the two eras is important as late effects researchers focus on complications and the attribution of radiation to late effects in future patients.

The clinical target volume margin – the anatomically defined margin surrounding the gross tumor volume – has varied considerably using photon therapy during the past two decades ranging from 2-10mm [73, 74] and depending on specific immobilization, verification, and delivery methods. The smallest target volume margins were used in highly-selected patients based on the physical limitations of the treatment devices and constrained to patients with small tumors < 6mm in diameter. More generalized conformal therapy methods including intensity-modulated photon therapy permitted treatment of larger tumors and the systematic study of target volume reduction. Understanding that the size and shape of the tumor may change during treatment in some patients and has made CP a leading indication for on-line and off-line imaging during irradiation including the use of MR imaging on a weekly basis or less often when imaging early in the treatment course demonstrates stability of the tumor

complex. The lack of cooperative or multi-institution clinical trials involving radiation therapy for CP has limited consensus on the appropriate target volume for irradiation; however, based on published reports and current listed trials the CTV margin for CP ranges from 3-5mm, most treating physicians will target both the post-operative tumor bed and residual tumor, and imaging at several time points during the treatment course and use image-guidance regardless of the modality (**Figure 3**).

There is a third aspect of basic clinical target volume definition that is now in evolution, the planning target volume. This margin surrounds the clinical target volume geometrically and is meant to account for variation in patient treatment set-up. Variability in patient set-up remains important for both photon and proton planning; however, the latter requires consideration of range uncertainty, which may vary on a beam by beam basis. Since very few beams are used with proton therapy and proton beams are more susceptible to changes in tissue path length robustness of proton treatment plans should include variability in target location as well as change in tissue composition and range calculation estimates. When prescribing proton therapy, there is an asymmetry to the final margin (planning target volume) that surrounds the previously defined clinical target volume.

Adverse effects of radiation therapy

The rationale for radiation therapy and its potential for side effects should be thoroughly understood by patients, their parents, and caregivers. Acute effects of radiation therapy are less concerning and when problematic related to treatment-induced cyst expansion. Most concerning is the broad impact of radiation therapy on cognitive function and the less common and potential more several complications vasculopathy and necrosis. The cognitive effects of radiation therapy are associated with patient age, sex, and key demographics as well as tumor and treatment-related factors [75] including the presence or absence of hydrocephalus that requires treatment, the extent of disease and resection, and radiation dose and volume. Similar to that observed following the treatment of other brain tumors, the impact of radiation therapy is greater in children under the age of 7-8 years and greatest in the very young. While

there is no limit concerning age at which irradiation may be administered in children with CP, the feasibility of surgery and other measures to delay or avoid irradiation should be considered for vulnerable patients. For those at increased risk for late effects, the most advanced forms of radiation therapy should be considered including pencil beam scanning proton therapy.

CP has become one of the more common indications for proton therapy. Children with CP can be rigorously immobilized, a requirement for proton therapy, and the relatively central location of the tumor and homogeneous tissue path from surface to target reduces some of the physical uncertainties related to proton range. These uncertainties must be accounted for in the planning and delivery process. However, the sensitivity of protons to changes in tissue path length can be a cause for concern in patients who rapidly gain or lose weight during treatment or when the cystic components of the tumor dynamically change the size and shape of the target. Early adopters of proton therapy that used the passive scattering method of delivery noted a significant change in the volume of normal tissue that received the lowest doses and unclear (no change or even a slight increase) benefit in the volume of normal tissue adjacent to the target that received the highest doses. Newer methods of proton therapy known as pencil beam or discrete spot scanning employ a magnetically positioned beam that delivers spots of protons, and therefore dose, to successive layers of the tumor as planned by treatment planning software and delivered by the energy selection and control systems of the proton accelerator and associated hardware. The difference is a more robust but less conformal passive scattering method compared to a less robust and highly conformal pencil beam scanning method [76] that reduces dose both adjacent to and at a distance from the target. Additional uncertainties of proton therapy related to linear energy transfer and radiobiological effectiveness demand careful monitoring of both common and less common complications and comparison with highly annotated photon clinical datasets. There are emerging data suggesting the equivalence of proton therapy compared to photon therapy with regard to vasculopathy, necrosis, and general neurological sequelae [77]. Investigators anticipate results supporting the hypothesis that cognitive outcomes are associated with radiation dose and

volume and that a reduction in critical combinations of radiation dose and volume achieved through the use of proton therapy will spare cognition in vulnerable patients.

In conclusion, CP has been a leading indication for proton therapy in children [78]. The ability of proton therapy to spare normal tissues from the volume that receives the lowest doses appears to be clear. That the reduction in the irradiated volume translates into improved outcomes for these patients remains uncertain and rests on the accumulation of prospective data assessing objective measures of CNS effects [79] and comparable patients treated with modern methods of photon irradiation. The results from early prospective trials should be available in 2017 [NCT01419067] (**Table 2**).

Long-term sequelae and prognosis

Patients with CP have a 3–19 fold higher cardiovascular mortality in comparison to the general population [7]. 20–year overall survival is impaired in patients with hypothalamic involvement of CP [80, 81]. Hypothalamic obesity has significant negative impact on long-term quality of survival [80, 82]. Increased daytime sleepiness, fatigue, disturbances of circadian rhythms [83-86] and eating behaviour [87-89], gastrointestinal and pulmonary complaints (diarrhea, dyspnea) [80], memory deficits [90, 91], (neuro)endocrine deficiencies [92], non-alcoholic fatty liver disease [93], and neuropsychological imbalances [94-100] are major long-term side effects in CP patients with hypothalamic obesity. Sterkenburg et al. [80] recently reported that hypothalamic involvement had a significant negative impact on 20-yr overall survival. The degree of surgical resection had no effect on 20-yr progression free survival rate in CP, supporting the concept that gross-total resection was of no advantage in terms of tumour recurrence (**Figure 4**).

Treatment of hypothalamic obesity

Due to disturbances in energy expenditure, central sympathetic output and appetite-regulation, CP patients with hypothalamic obesity typically develop morbid obesity that is

mainly unresponsive to conventional lifestyle modifications [1, 101-103]. Recent studies on novel pharmaceutical treatment options in CP patients with hypothalamic obesity report mixed results. Based on impairment of sympatho-adrenal activation and epinephrine production manifesting as a reduced hormonal response to hypoglycaemia, treating this disorder with amphetamine derivatives has been suggested [104]. Zoicas *et al* [105] treated 8 adult patients (6 CP) with hypothalamic obesity with GLP-1 analogues and observed a substantial and sustained weight loss associated with improvements in metabolic and cardiovascular risk profiles.

Daubenbüchel et al. [106] recently reported that CP patients are able to produce and secrete the hormone oxytocin, even when pituitary and hypothalamic structures were damaged. However, patients with hypothalamic damage grade 1, which involves damage only to the anterior hypothalamic areas, presented with a lower fasting level of oxytocin. In addition, changes in oxytocin levels before and after standardized breakfast correlated with BMI, demonstrating that CP patients with hypothalamic obesity show less variation in oxytocin secretion due to nutrition. Accordingly, the authors speculate that oxytocin supplementation might be a therapeutic option in CP patients with hypothalamic obesity and/or neurobehavioral deficits due to specific hypothalamic damage in the anterior hypothalamic area.

Initial experiences with bariatric surgery in severely obese CP patients achieved sufficient tolerability and short-term weight reduction [107-109]. An instant improvement of binge-eating behaviour in patients immediately after laparoscopic adjustable gastric banding (LAGB) was observed, but failed in long-term weight reduction. Treatment with invasive, non-reversible bariatric methods such as Roux-en-Y gastric bypass is most efficient in weight reducing [107] but controversial in the paediatric population due to medical, ethical and legal considerations [109].

Despite the availability of promising therapeutic approaches [27], it must be emphasized that currently no generally accepted therapy for hypothalamic obesity in CP has been shown to be effective in randomized studies.

Risk-adapted treatment strategies

Risk-adapted treatment strategies [53, 55, 96, 110-119] are focusing on the following main goals: (a) reversal of visual compression symptoms, (b) relief of raised intracranial pressure, (c) prevention of tumor regrowth/progression, and (d) restoration or substitution of pituitary hormone deficits plus all other supplement-supportive measures, while minimizing acute and long-term mortality and morbidity [1, 102, 120] (**Table 3**).

De Vile *et al.* [121] published the first reports on the association between attempts at radical gross total resection in case of hypothalamic involvement and long-term morbidity. Puget *et al.* [53, 111] published an algorithm for surgical treatment of CP patients, which recommends a hypothalamus-sparing strategy based on a grading of hypothalamic tumor involvement in preoperative magnetic resonance imaging (MRI) [53]. The same authors reported that patients neurosurgically treated according to this algorithm using a hypothalamus-sparing approach had similar relapse rates and a lower prevalence of severe obesity than patients treated by gross-total resection (28% versus 54%, respectively) [111]. This was the first report in the literature proving the tolerability and efficacy of a hypothalamus-sparing strategy by comparing cohorts treated by the same experienced surgical team at a single institution, and thus eliminating the bias of surgical experience on outcome analysis. However, it is important to note that although the "hypothalamus-sparing surgery" increased the percentage of "normal" body mass index (BMI) from 17–38%, the likelihood of clinically significant weight gain remained 62% with nearly half of all patients developing morbid obesity. Müller *et al.* [112, 113] published studies on a risk-adapted treatment strategy based on pre- and post-surgical grading of hypothalamic involvement/damage in MRI. The assessment of the suprasellar tumor extension towards the mammillary bodies is considered essential for their grading into anterior or posterior hypothalamic involvement/lesion. According to their report, patients with post-surgical lesions affecting posterior hypothalamic structures presented with increased BMI and reduced self-assessed quality of survival during long-term prospective follow-up (**Figure 5**). Mallucci *et al.* [55] published a treatment algorithm, suggesting a two-staged surgical approach with initial relief of cystic pressure and thereby down-staging the risk grade in appropriate cases.

Since the majority of patients in these studies come from low volume or low experience centers, the long-term outcome data may be more applicable to "community practice" than applicable to high volume surgical centers. Even though the Paris series [111] represents a large volume center, it is still a single institutional, sequential study and not multi institutional, randomized, or even case controlled.

All of the above-mentioned treatment strategies and algorithms recommend that (a) for CP with hypothalamic involvement, limited surgical approaches and postoperative external irradiation are advisable, and (b) treatment of CP should be confined to experienced multidisciplinary teams.

A major step towards potential standardization of preoperative staging in CP is the comparison of published grading systems for assessment of hypothalamic damage/involvement in regard to prediction value for severe hypothalamic obesity as the main sequelae impairing quality of survival. Mortini *et al.* [118] analyzed the sensitivity of three published grading systems [111-114] for prediction of hypothalamic obesity in their single center cohort. Variables identified as factors with high and comparable prediction value for postoperative hypothalamic syndrome were the degree of hypothalamic involvement according to the classification described by Sainte-Rose and Puget [111], Van Gompel *et al.* [114], and Muller *et al.* [112, 113]. These results support the hypothesis that disease or treatment-related hypothalamic alterations have relevant negative impact on quality of survival and prognosis in CP [2, 122].

There are only a few studies analyzing the prognosis of patients with CP in relation to the neurosurgeons' experience [53, 112, 113, 123-126]. Sanford [123] and Boop [124] reported clinically significant differences in outcome according to the neurosurgeons' experience with the condition. Degree of obesity and quality of life were analyzed in a recent report based on reference assessment of tumor location and post-surgical hypothalamic lesions [113]. Treatment was also analyzed regarding neurosurgical strategy and the neurosurgical center sizes based on patient load. Surgical lesions of anterior and posterior hypothalamic areas were associated with post-surgical obesity, negatively impacting long-term quality of survival in patients with

surgical posterior hypothalamic lesions [112, 113]. Treatment strategies in large centers were less radical and the rates of complete resection and hypothalamic surgical lesions were lower than those of middle and small-sized centers [112, 113, 126]. However, in multivariable analysis preoperative hypothalamic involvement was the only independent risk factor for severe obesity [113].

For favourably localized CP, the preferred treatment of choice, especially at initial diagnosis, is an attempt at complete resection with preservation of hypothalamic and visual function [1, 102, 111, 125, 127-130]. For unfavourably localized tumours – those too close to or too entangled with the hypothalamus and/or the optic chiasm – a limited resection followed by irradiation should be considered in order to preserve integrity of and/or to avoid further damage to optic and hypothalamic structures [126, 131-138].

Overall, surgical results reported by the most experienced /skilled surgeons after gross total removal of CPs (combining children and adults) coincide in an extremely low mortality (0-5%) and low morbidity rates due to hypothalamic damage (around 10-15% on average). This is in apparent contradiction with the extreme heterogeneity regarding the pathological and clinical expression of these lesions and the common consideration of CPs as one of the most challenging lesions for the neurosurgeon in lectures as well as in personal communications. Everybody communicates dreadful experiences with individual CP cases, never reported in official journals. Surgical results should be improved with the learning curve effect (as reported by Yasargil et al. [47]), but this effect seems negligible in recent publications. The honesty showed by the Necker's team by changing their CP treatment paradigm to limit the surgical risks associate with hypothalamic injury must be appreciated.

However, CPs represent the paradigm of an individual, multifaceted complex type of lesion which treatment should never be planned under the "rules" of a fixed protocol, independently of how experienced/skilled the team/surgeon/radiotherapist may be. In this sense, any approach of CPs as a "disease" or "common pathological entity" is misleading, as comparisons between series including lesions with different topographies, sizes, shapes, consistencies, histologies, clinical impairments, will not allow sound results nor warrant the

desired outcome for an individual patient. No proper characterization of the subset of adamantinomatous CPs in the children population versus the adult population has been provided up to date. However, given the rarity of these lesions it is the personal cautiousness and time inverted in gaining the maximal knowledge about every individual case, more than any dogmatic criteria established by a professional/political "authority" what makes the difference for each patient.

Conclusions:

In conclusion, the molecular pathogenesis of human adamantinomatous CP has started to be unveiled offering the possibility of testing novel treatments targeting pathogenic pathways. Several pre-clinical models are available, which although not perfect, are suitable tools to investigate the role of these pathways in tumour biology and determine their therapeutic potential against human adamantinomatous CP.

Proton therapy clearly reduces collateral radiation dose to normal tissue when compared with photon (X-ray)-based methods of irradiation. Preliminary results from first generation trials using proton therapy are anticipated.

Hopefully, published grading systems support efforts in establishing standards for staging in CP, which should be implemented by national and international societies. Gross-total resection should be avoided in CP with hypothalamic involvement to prevent further hypothalamic damage. As surgical expertise has been shown to have impact on postoperative morbidity, medical societies should establish criteria of adequate professional expertise for the treatment of CP. Based on these criteria, health authorities should organize the certification of centers of excellence authorized for treatment and care of patients with this chronic disease.

Review criteria

A search for original articles published between 2000 and 2016 that focused on childhood craniopharyngiomas was performed in PubMed, Science Citation Index Expanded, EMBASE

and Scopus. The search terms used were “craniopharyngioma”, “hypothalamus and obesity”, pituitary and obesity”, radiation oncology”, and “neurosurgery”. We also searched the reference lists of identified articles for further papers.

Key points:

- The clinical, neuroradiological and surgical definition of hypothalamic involvement is a fundamental factor related to postoperative poor outcome, progressive obesity and neuropsychological impairment in the child after surgical removal of CP.
- There is a need to change the previously assumed “gold-standard” objective of a primary radical removal of the lesion in all cases by the new paradigm of a limited resection plus focused radiotherapy in CP patients with hypothalamic lesions.
- Hypothalamic involvement and treatment-related hypothalamic lesions are associated with the highest risk of postoperative sequelae and impaired quality of survival.
- Three dimensional intensity modulated proton beam radiotherapy has potential advantage of over photon beam methods to focus and limit the radiation effects to optic and hypothalamic structures.
- Pre-clinical, in vivo mouse model of adamantinomatous CP have potential advantage to investigate the intracellular molecular pathways deregulated in the tumor and to test the use of specific drugs.

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Figure 1

Genes and molecular pathways involved in human ACP. Schematic outlining majorly deregulated genes and pathways in ACP, resulting from activating mutations in beta-catenin. Most, if not all ACP tumours carry mutations in *CTNNB1* (beta-catenin) directly resulting in the over-activation of the WNT/beta-catenin pathway. This is evidenced by the expression of target genes such as *AXIN2* and *LEF1*. As the result of this initial oncogenic hit, defined as the driver mutation, several further genes and pathways become deregulated. These are likely to affect multiple biological processes such as cell proliferation, survival, differentiation, inflammation, angiogenesis, cell adhesion and tumour infiltration among others. The colour code indicates the potential involvement of the deregulated pathways in these biological processes, as deducted from other cellular/tumoural contexts. This assessment is not exclusive as many of the pathways may be involved either directly or indirectly in several or all of the processes indicated. Knowing whether the inhibition or stimulation of some of these pathways may be of therapeutic use requires robust pre-clinical data to confirm their pathogenic effects. For more details, see references [20, 24, 27, 30-33]

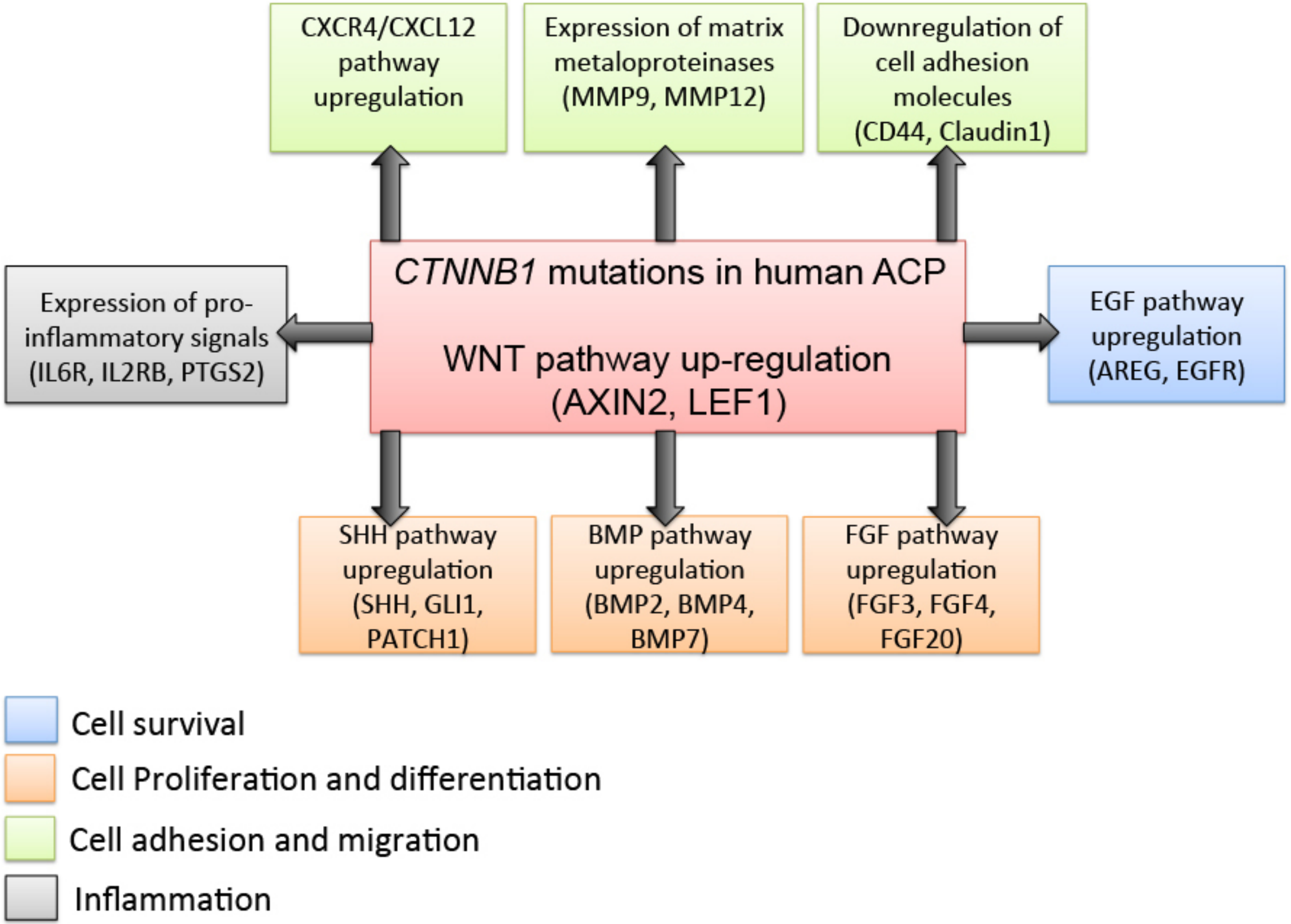
CXCR4/CXCL12 pathway upregulation
Expression of matrix metaloproteinases (MMP9, MMP12)
Downregulation of cell adhesion molecules (CD44, Claudin1)
CTNNB1 mutations in human ACP
WNT pathway up-regulation (AXIN2, LEF1)
Expression of pro-inflammatory signals (IL6R, IL2RB, PTGS2)
EGF pathway upregulation (AREG, EGFR)
SHH pathway upregulation (SHH, GLI1, PATCH1)
BMP pathway upregulation (BMP2, BMP4, BMP7)
FGF pathway upregulation (FGF3, FGF4, FGF20)
Cell survival
Cell Proliferation and differentiation
Cell adhesion and migration
Inflammation

Figure 2:

Paracrine model for the involvement of pituitary stem cells in tumorigenesis. (i) Schematic representation of Sox2+ve stem cells (A) and Sox2-ve cells in the adult pituitary. Expression of oncogenic β-catenin in some Sox2+ve cells (A* in ii) results in transient proliferation and formation of β-catenin-accumulating cell clusters (A* in iii-vi) and the release of secreted factors to the surrounding cells (iii) leading to cell transformation (B'), proliferation (B' in v) and tumour formation (B' in vi).

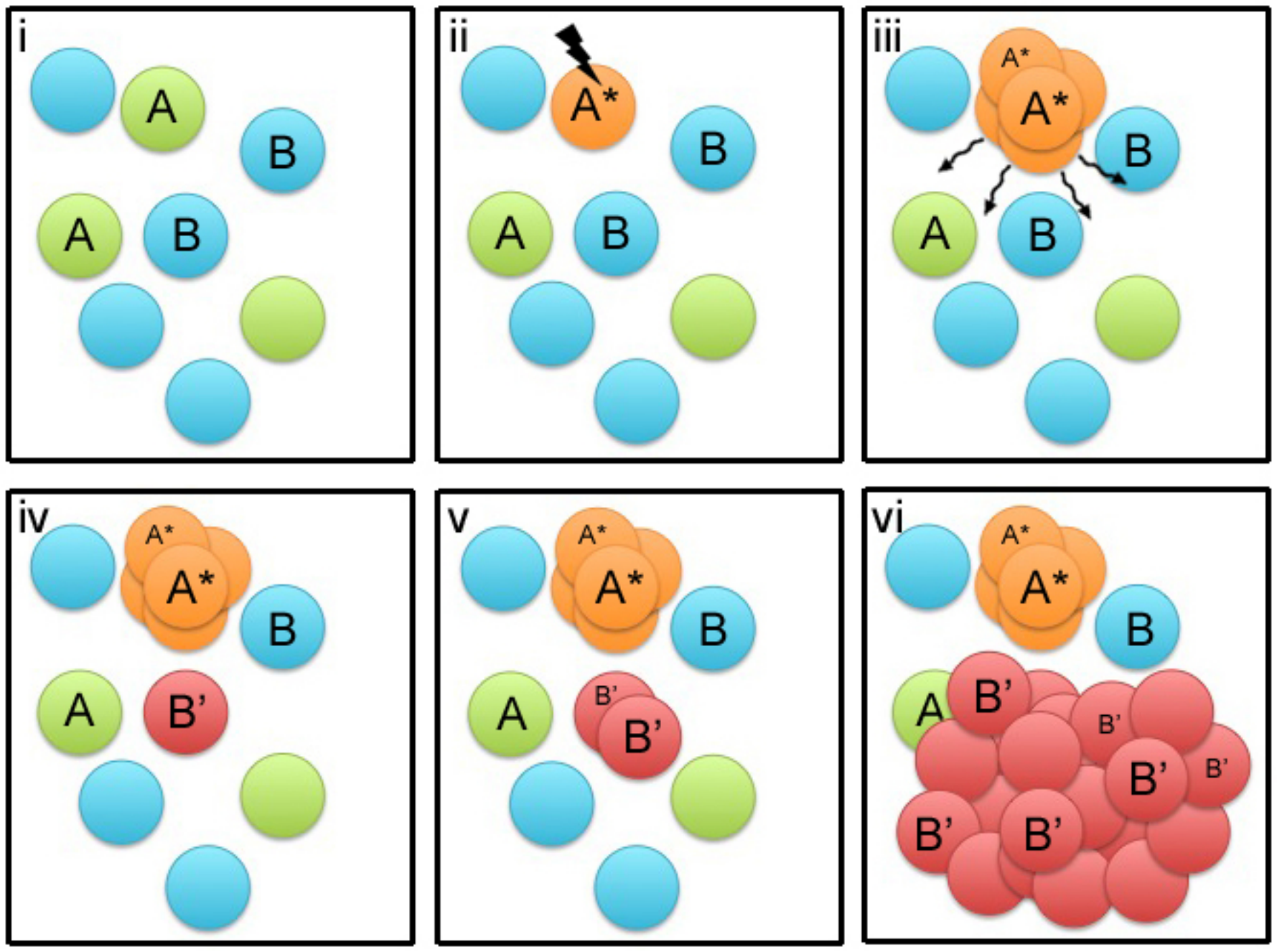
i
A
B
A
B
ii
A*
B
A
B
iii
A*
A*
B
A
B
iv
A*
A*
B
A
B’
v
A*
A*
B
A
B’
B’
vi
A*
A*
B
A
B’
B’
B’
B’
B’
B’
B’

Figure 3

The figure shows an image of a sagittal CT with color-wash proton dose distribution in a child with craniopharyngioma. Bone defect present in base of skull after trans-nasal surgery and calcifications present in third ventricle corresponding to unresected tumor. Color legend: orange-red = 50.4-54CGE; dark blue ≤ 10.8CGE.

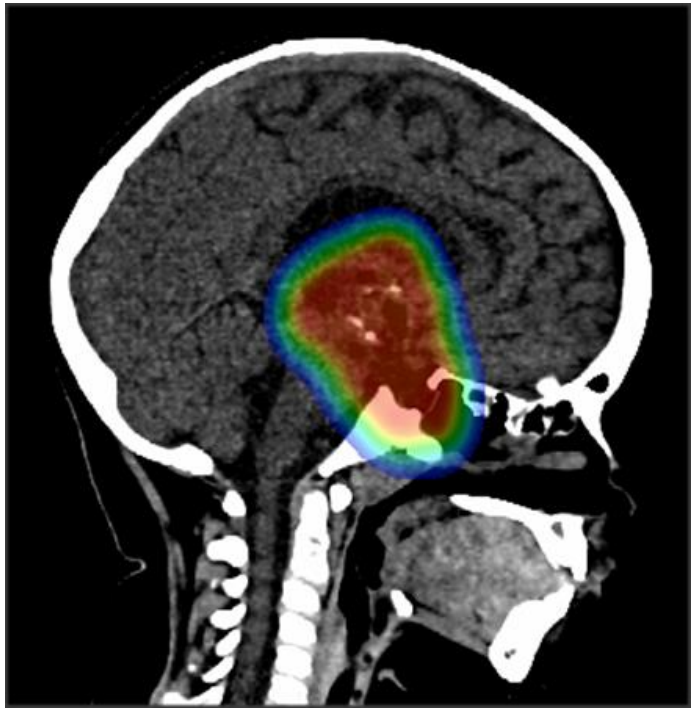

Figure 3

Figure 4

Twenty-yr overall survival in regard to hypothalamic involvement (Figure 4A) and 20-yr progression-free survival (PFS) in regard to the degree of surgical resection (Figure 4B) of patients with childhood-onset craniopharyngioma recruited in the trial HIT Endo. CR=complete resection; IR=incomplete resection; as confirmed by neuroradiological reference assessment. Reproduced and modified from Sterkenburg et al. [80] with kind permission of Oxford University Press.

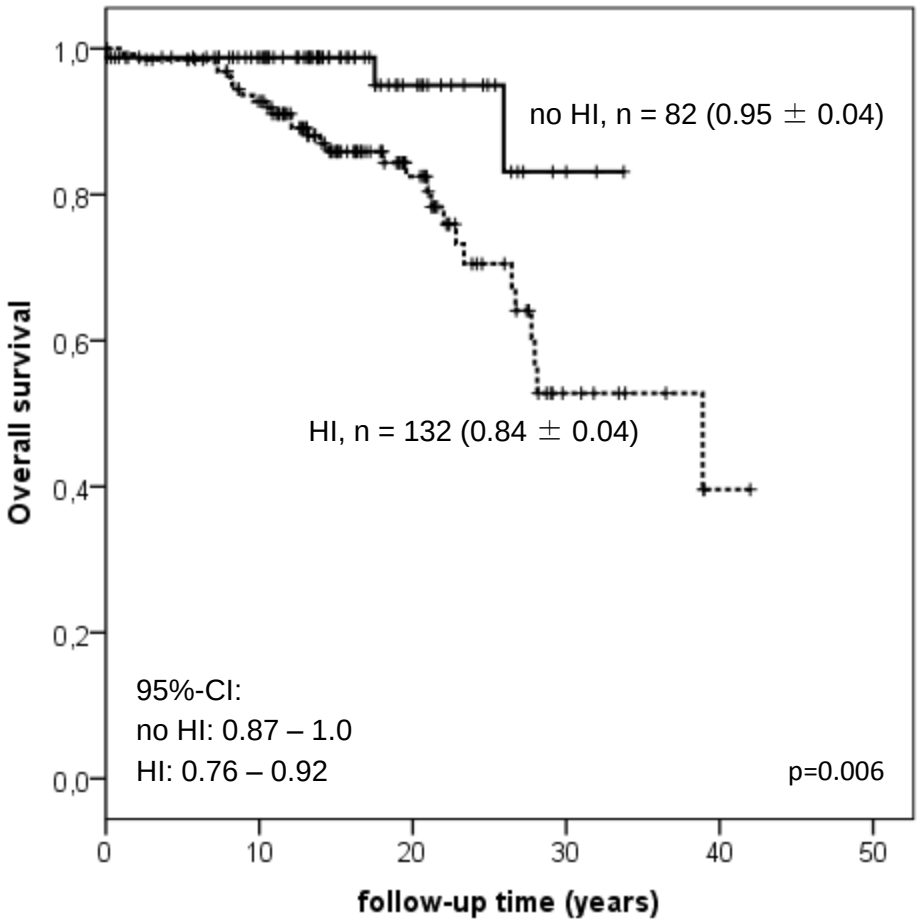
1,0
0,8
0,6
0,4
0,2
0,0
Overall survival
no HI, n = 82 (0.95 ± 0.04)
HI, n = 132 (0.84 ± 0.04)
95%-CI:
no HI: 0.87 – 1.0
HI: 0.76 – 0.92
p=0.006
0
10
20
30
40
50
follow-up time (years)

Figure 4A

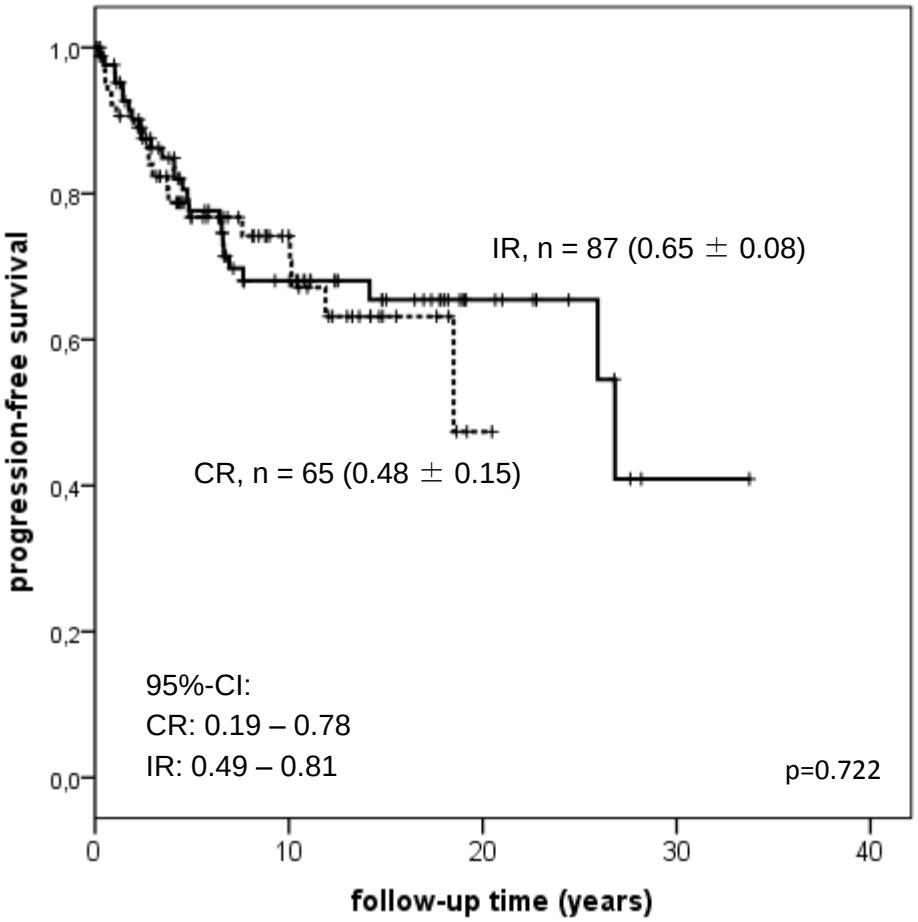
progression-free survival
1,0
0,8
0,6
0,4
0,2
0,0
0
10
20
30
40
follow-up time (years)
IR, n = 87 (0.65 ± 0.08)
CR, n = 65 (0.48 ± 0.15)
95%-CI:
CR: 0.19 – 0.78
IR: 0.49 – 0.81
p=0.722

Figure 4B

Figure 5

BMI and MRI imaging at diagnosis and 36 months after surgery in three cases of childhood craniopharyngiomas (CP) with different grade of hypothalamic involvement/lesion. (a and b) Patient with CP confined to the intrasellar space (0o no hypothalamic involvement (a)/surgical lesion (b)). BMI at diagnosis: –1.96 S.D.; BMI 36 months after complete resection: –1.62 S.D. (c and d) Patient with CP involving the anterior hypothalamus (Io hypothalamic involvement (c)/surgical lesion of the anterior hypothalamic area (d)). BMI at diagnosis: +1.01 S.D.; BMI 36 months after complete resection: +0.59 S.D. (e and f) Patient with CP involving the anterior and posterior hypothalamus (II^0 hypothalamic involvement (e)/surgical lesion of the anterior and posterior hypothalamic area (f)). BMI at diagnosis: +6.08 S.D.; BMI 36 months after complete resection: +6.79 S.D. Mammillary bodies are defining the border between anterior and posterior involvement/lesion. Figure 3 e,f modified and reproduced from Müller et al. [113] with permission of Bioscientifica.

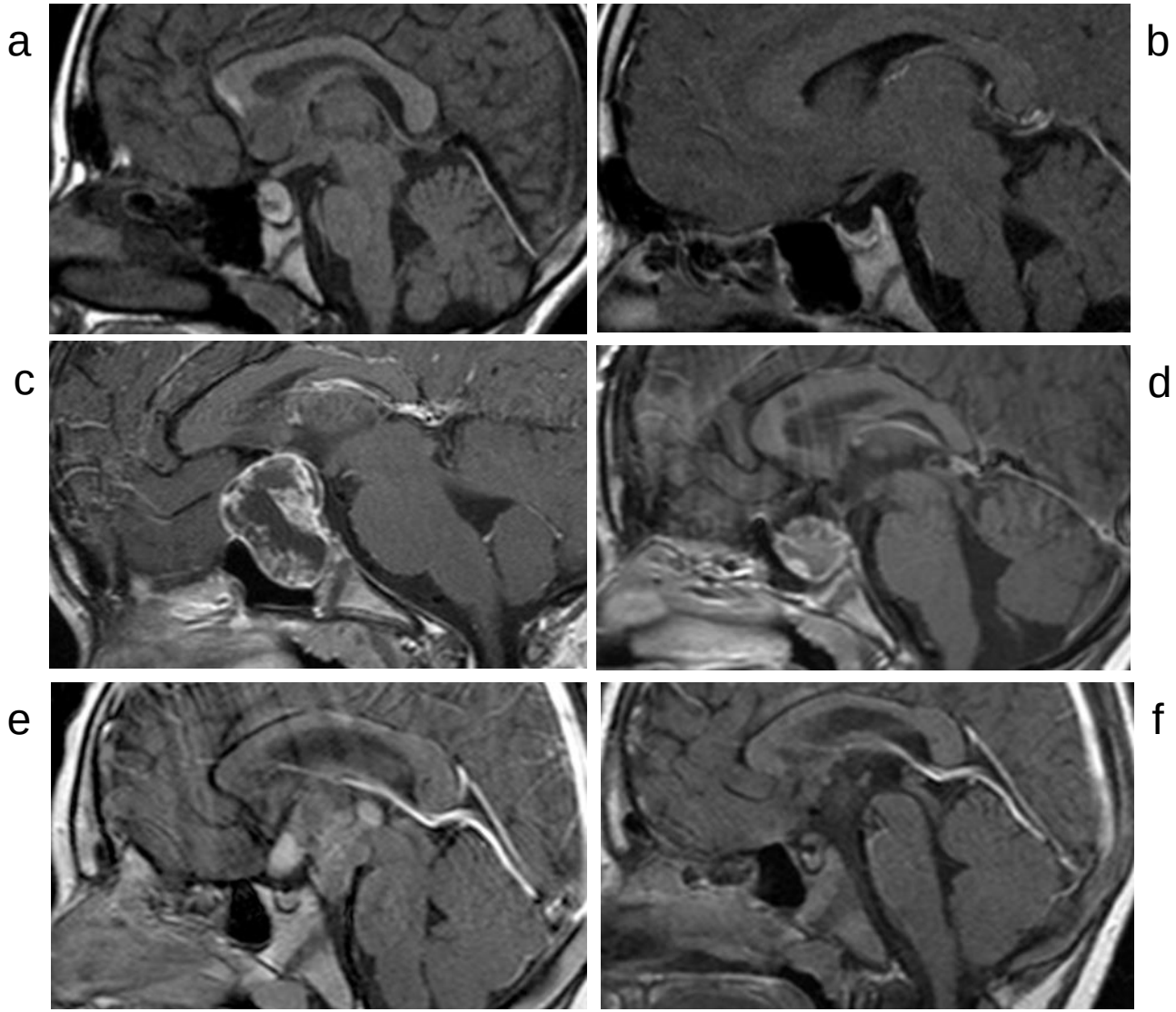

Figure 5

Table 1

Comparison of available pre-clinical models of human adamantinomatous craniopharyngioma. GEMMs: Genetically modified mouse models; PDXs: Patient-derived xenografts; Origin: The origin of the tumour cells; Availability: Primary cells are not immortalized, so as PDXs, availability is restricted to biopsies, which are rare; Tumour location: GEMMs‘ tumours develop intracranially. PDXs have been generated intracranially and subcutaneously; Growth: PDXs and primary cells show very slow growth; Cellular architecture: GEMMs’ tumours show only some histological similarities to human ACP, whilst PDXs are identical to the human neoplasias; Brain Blood Barrier (BBB): GEMMs’ tumours develop outside the BBB. PDXs’ tumours grow either within (e.g. cortex) or outside (e.g. subcutaneously) the BBB; Tumour/host interactions: PDXs develop in immunosuppressed mice.

Table 1

Comparison of available pre-clinical models of human adamantinomatous craniopharyngioma.

	Primary cells	GEMMs	PDXs
Origin	Human	Mouse	Human
Availability	Difficult	Easy	Difficult
Tumour location	-	Orthotopic	Orthotopic/heterotopic
Growth	Slow	Fast	Slow
Preserved cellular architecture	-	Partial	Identical
BBB penetrance problems	-	No	Yes/No
Tumour/host interactions	-	Yes	No

Table 2

Advantages and disadvantages of modern radiotherapy methods used in the treatment of craniopharyngioma

Table 2

Technology	Advantages	Disadvantages
Conventional 2-D radiotherapy	Reliable clinical data and long-term follow-up indicating high efficacy of radiotherapy.	Poor geometrical precision. No reliable protection of normal surrounding tissues.
Fractionated conformal radiation therapy/IMRT	Widely available, highly conformal, ease in adapting treatment to changing target.	Highly conformal photon therapy requires exposure of a larger volume of normal tissue to low doses of radiation.
Fractionated proton therapy	Normal tissue sparing. The volume or normal tissues exposed to low doses is significantly less compared to fractionated photon methods.	Limited experience and significant costs. Image-guidance systems have lagged. Early passive scattering systems provided robust treatment yet lacked conformity of advanced photon systems. Newer pencil beam scanning systems require evaluation in clinical trials.
Radiosurgery	Single treatment session. Highly conformal. Almost no dose to non-target tissue.	Limited indications and experience. Only suitable for small volume solid residual and when tumor is not in contact with vital structures such as optic chiasm.
Hypofractionated image guided radiosurgery (CyberKnife)	Fewer treatment sessions. Highly conformal.. May have biological advantages under certain conditions.	Very limited indications and experience. Role still unclear. No reliable data for tumor control or side effect reduction.
Intracavitary colloid isotope application	High tumor control rates for cystic components. Applicable to tumors recurrent after prior irradiation.	Advantages limited to cystic tumors. Underdosage of solid components. Complications related to leakage or high-doses when administered in proximity to vital structures such as visual pathways and brainstem.

Table 3

Novel grading systems and treatment algorithms for craniopharyngioma patients based on magnetic resonance imaging. n, size of cohort; FU, follow-up; HI, hypothalamic involvement; HD, hypothalamic damage; n.a., not analyzed; HUI, Health Utility Index; GTR, gross-total resection; STR, subtotal resection; MB, mammillary bodies; XRT, irradiation; BMI, body mass index; TGTV, growth towards 3rd ventricle; MRI, magnetic resonance imaging; w/o, without; ped, pediatric patients.

Table 3:

Author	n	FU (yr)	Grade **0** (0^o)	Grade 1 (I^o)	Grade 2 (II^o)	Treatment recommendation	Outcome parameters
Puget[53]	66 ped	7	No HI	Contact with HI (distortion/ elevation) the hypothalamus is still visible	Tumor spread to the hypothalamus, which was no longer identifiable.	**0^o**: GTR **I^o**: GTR; if not achieved: 2^{nd} OP ± XRT **II^o**: STR w/o HD + XRT	Grading correlated with BMI, HUI, neuropsycho-logical disorders
Elowe-Gruau[111]	65 ped	3	No HI	Contact with HI (distortion/ elevation) the hypothalamus is still visible	Tumor spread to the hypothalamus, which was no longer identifiable.	**0^o**: GTR **I^o**: GTR; if not achieved: 2^{nd} OP ± XRT **II^o**: STR w/o HD + XRT	Lower BMI in cohort treated per algorithm
Müller [112, 113]	120 ped	3	No HI	HI/HD of the anterior hypothalamus not involving MB	HI/HD of the anterior + posterior hypothalamic area, i.e., involving MB	**0^o**: GTR **I^o**: STR w/o HD + XRT **II^o**: STR w/o HD + XRT	Higher BMI and lower QoL in II^o cohort treated by GTR with posterior HD
Fjalldal [96]	42 ped	20	No HI	Suprasellar growth, not towards or into the 3^{rd} ventricle (non-TGTV)	Suprasellar growth towards or into the 3^{rd} ventricle (TGTV)	**Non-TGTV**: GTR **TGTV**: STR w/o HD + XRT	Lower cognitive performance in TGTV patients treated by GTR
Van Gompel[114]	28 adults	1	No HI	Degree of hypothalamic T2 signal change and irregular hypothalamic contrast enhancement in MRI		Risk-adapted surgical strategies according to MRI findings on HI	Post-OP weight gain corre-lated with degree of HI
Elliott[115]	80 ped	9	Preoperative clinical status assessed with standardized scale (CCSS) including vision, pituitary function, hypothalamic dysfunction, educational/occupational status			Risk-adapted surgical strategies according to preoperative CCSS findings	Pre-OP CCSS predicted outcome better than MRI-assessed HI/HD
Steno[116]	41 ped	10	No HI	Outside the 3^{rd} ventricle	Inside the 3^{rd} ventricle	GTR only in case of location outside the 3^{rd} ventricle recommended	Better outcome after GTR in extraventricular cases
Mallucci [55]	20 ped	3	No HI	Tumor size (<2–4cm), no hydrocephalus, no breech 3^{rd} ventricle	Retrochiasmatic tumor, (>4cm), hydrocephalus, breech 3^{rd} ventricle	**0^o**: GTR **I^o**: consider GTR **II^o**: STR w/o HD + XRT	Reassessment of HI after endoscopic cyst shrinkage, improved surgical strategy
Roth[117]	41 ped	5	No HI	HD score including assessment of pituitary gland and stalk, ventriculomegaly, and residual tumor		Risk-adapted surgical strategies according to HD score	HD score correlated ($p=0.02$) with BMI post OP
Mortini [118]	47 20% ped	3.2	Grade of HI according to hypothalamic hyperintensity in T2-weigh-ted MRI, MB involvement, unidentifiable pituitary stalk, dislocated chiasm, unrecognizable supraoptic recess, retrochiasmatic extension			Risk-adapted surgical strategies according to grade of HI	Outcome related ($p<0.01$) to published grading systems [53, 112, 113]