Craniopharyngioma

Hermann L. Müller[1]*, Thomas E. Merchant[2], Monika Warmuth-Metz[3],

Juan-Pedro Martinez-Barbera[4] and Stephanie Puget[5]

[1]Department of Pediatrics and Pediatric Hematology/Oncology, University Children's Hospital, Klinikum Oldenburg AöR, Oldenburg, Germany

[2]Department of Radiation Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee, USA

[3]Department of Neuroradiology, University Hospital, Würzburg, Germany

[4]Developmental Biology and Cancer Programme, Birth Defects Research Centre, UCL Great Ormond Street Institute of Child Health, University College London, London, UK

[5]Service de Neurochirurgie, Hôpital Necker-Enfants Malades, Sorbonne Paris Cité, Paris, France

***email:** mueller.hermann@klinikum-oldenburg.de

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Abstract

[Au: shortened to fit; please check carefully]

Craniopharyngiomas are rare embryonic malformational tumours of low histological malignancy arising along the craniopharyngeal duct. The two histological subtypes, adamantinomatous craniopharyngioma (ACP) and papillary craniopharyngioma (PCP), differ in genesis and age distribution. ACPs are diagnosed with a bimodal peak of incidence (5–15 years and 45–60 years) whereas PCPs are restricted to adults mainly in the fifth and sixth decade of life. ACPs are driven by somatic mutations in *CTNNB1* (encoding β-catenin) that affect β-catenin stability and are predominantly cystic in appearance. PCPs frequently harbour somatic *BRAF-V600E* mutations and are typically solid tumours. Clinical manifestations due to increased cerebral pressure, visual impairment and endocrine deficiencies should prompt imaging investigations, preferentially MRI. Treatment comprises neurosurgery and radiotherapy; intracystic chemotherapy is used in monocystic ACP. Although long-term survival rates are high, quality of life and neuropsychological function are frequently impaired due the close anatomical proximity to the optic chiasm, hypothalamus and pituitary gland. Indeed, hypothalamic involvement and treatment-related hypothalamic lesions frequently result in hypothalamic obesity, physical fatigue and psychosocial deficits. Given the rarity of these tumours, efforts to optimize infrastructure and international collaboration should be research priorities. **[Au:OK?]**

[H1] Introduction

Craniopharyngioma (CP) is a rare brain tumour managed primarily with surgery and radiotherapy[1-3]. Due to their embryonic origin from remnants of the craniopharyngeal duct epithelium (known as Rathke's pouch, **which is an invagination at the roof of the developing mouth that gives rise to the anterior pituitary gland [Au:OK?] YES**), CPs are located **which is an invagination at the roof of the developing mouth that gives rise to the anterior pituitary gland** either in the sella turcica (that is, the depression in the sphenoid bone, containing the pituitary gland; intrasellar) or above the sella turcica (suprasellar) **[Au:OK?]**. Although CPs may develop at any point along the pituitary–

hypothalamic axis, from the sella turcica to the third ventricle of the brain, ~50% originate at the level of third ventricle floor, within the infundibulum and/or tuber cinereum regions (including the vital hypothalamus), and predominantly expand to the third ventricle cavity. Appropriate awareness of the close contact between these lesions and the hypothalamic nuclei is fundamental to avoid an undue hypothalamic injury[4]. Extremely rarely, CPs can occur in different locations such as the cerebellopontine angle; the origin of such tumours remains unclear although a high proportion of these **[Au:OK?]** so-called ectopic CPs have been observed in individuals with Gardner syndrome (an autosomal dominant polyposis)[5].

[Au: new paragraph] Unlike malignant tumours, CPs do not disseminate but cases of spinal spread due to intraoperative 'spill' of tumour material have been documented[6]. In children, a combination of the symptoms including headache, visual impairment, growth retardation and polyuria–polydypsia due to central diabetes insipidus (whereby deficiency of arginine vasopressin from the pituitary gland or hypothalamus leads to production of hypotonic urine) **[Au:OK to define as 'central' DI and with this description?]** is highly indicative of CP. In adults, endocrine deficiencies such as impaired sexual function, clinical manifestations of increased intracranial pressure (such as headache) and hypothalamic syndrome (such as disruptions in body temperature regulation, growth and water balance) **[Au: text in brackets added ok?]** are major symptoms. Although CPs are typically of low histological grade (that is, WHO grade I), the prognosis and outcomes of patients are frequently impaired owing to the hypothalamic–pituitary location of the CP and tumour-related and/or treatment-related injury to these areas.

The two histological subtypes of CP, adamantinomatous craniopharyngioma (ACP) and papillary craniopharyngioma (PCP), differ in their genesis and age distribution (Figure 1). ACPs affect all age groups and are the more common subtype, PCPs are mostly restricted to adults[7]. ACPs are driven by somatic mutations in *CTNNB1* (encoding β-catenin) that increase β-catenin stability leading to the activation of the WNT pathway and have been proposed to be of embryonic origin based on molecular and histological features[8-11]. By contrast, PCPs frequently harbour somatic *BRAF-V600E* mutations

that result in the activation of the MAPK signalling pathway[11-13] **[Au: are they not also embryonic in origin? NO]**. The typical combination of imaging features of ACPs can be described using the so-called 90% rule — whereby ~90% of tumours are predominantly cystic, ~90% show typically **[Au:OK?]** prominent calcifications and ~90% take up contrast media in the cyst walls[14, 15]; PCPs are more frequently non-calcified and 'solid'.

In the early 20th century, surgery for sellar masses such as CP was extremely challenging and risky owing to their close anatomical proximity to the optic chiasm and hypothalamic–pituitary axis. With the introduction of microscopy, antibiotics and corticosteroids, prognosis and surgical outcome after CP have improved substantially. Progress in the field of neuroradiological imaging, surgical techniques and radiotherapy **[Au: edited for brevity ok?]** have improved tumour control and reduced complications. **[Au: merged paragraphs]** Current treatment strategies are debated **[Au:OK?]**, ranging from radical surgical strategies such as gross-total resection (GTR) and the extended trans-sphenoidal endoscopic endonasal approach (EEA) to limited surgical approaches focused on the preservation of hypothalamic and visual integrity and quality of life (QOL) after treatment[1-3, 16-30] **[Au: We can't include so many references in one shot as online they will be listed individually to enable click-through to the reference list, taking up considerable space. As these points will be discussed in more detail later, please cite no more than 5 references here]**. Additionally, radio-oncological approaches and techniques such as proton beam therapy have an important role in the management of CP[31]. However, safe GTR remains the goal when feasible (that is, when hypothalamic integrity can be preserved) and is associated with the highest recurrence-free survival[26].

The low incidence of CP, and dissimilarity in presentation, location and treatment compared with more common brain tumours, limits our knowledge, expertise and management options **[Au:OK?]**. Although these challenges may not affect overall survival, the rate of treatment-related complications and functional outcomes are likely to be affected. Issues such as definition and implementation of criteria at treatment centres of excellence are important owing to the association with outcomes, and understanding pathogenetic mechanisms and neuropsychological late effects as a basis for risk-

adapted therapy and rehabilitation is warranted. This Primer presents the current concepts of pathogenesis, diagnostics, multidisciplinary treatment and follow-up care in CP.

[H1] Epidemiology

CPs constitute 1.2–4.6% of all intracranial tumours, accounting for 0.5–2.5 new cases per 1 million population per year, globally[32-34], although CPs are more frequent in Japan for reasons that are unclear **[Au:OK?]**, with an annual incidence of 3.8 cases per 1 million children[35]. Of patients with CPs, 30–50% are diagnosed during childhood and adolescence[32]. CPs are the most common non-neuroepithelial intracerebral neoplasm in children (<18 years of age) accounting for 5–11% of intracranial tumours in this age group[33, 36-41] **[Au: if we can reduce the number of references here, please consider doing so]**.

ACP **[Au:OK?]** has a bimodal age distribution[34, 42], with peak incidences in children aged 5–15 years and adults aged 45–60 years. In the childhood and adolescent age group, the APC histological type with cyst formation is most common[43, 44]. Rare neonatal and fetal cases have been reported[43, 45, 46]. PCPs occur almost exclusively in adults, at a mean patient age of 40–55 years[47]. In population-based studies, no sex differences have been observed[32, 48]. **[Au: 'Hereditary'?]** CP cases have been reported within two families[49, 50], but an underlying genetic susceptibility has not been verified.

[H2] Survival and late morbidity

Overall mortality rates in CP are reported to be three to five times higher than those observed in general population[51]. Overall survival described in paediatric cohorts ranges from 83% to 96% at 5 years[52], from 65% to 100% at 10 years[53, 54] and on average 62% at 20 years. In mixed paediatric and adult patient cohorts, overall survival is in the range of 54% to 96% at 5 years[51, 55], 40% to 93% at 10 years [51, 55, 56] and 66% to 85% at 20 years[51, 56]. Whether age at diagnosis of CP is a prognostic factor for survival is still a matter of debate. Several studies have shown that the youngest patients experience better survival rates **[Au: than adolescent and adult patients?]**[57, 58], but others report better outcomes in older patients with CP or similar survival rates in paediatric and adult cohorts[32, 55]. Some authors have observed higher mortality among female patients[51], whereas others did not find any sex

differences in terms of survival[55]. Furthermore, a better prognosis for PCPs compared with ACPs has been reported[59, 60], but other studies have not replicated this finding **[Au:OK?]**[47, 61].

Late morbidity **[Au: what is the definition of 'late' here? How many years after primary treatment or primary diagnosis?]** is associated with tumour-related and/or treatment-related risk factors such as progressive disease with multiple recurrences, cerebrovascular disease (such as fusiform dilatations of the carotid artery[62]) and chronic neuroendocrine deficiencies[53, 54, 63-65]. Additionally, non-alcoholic fatty liver disease leading to liver cirrhosis has been reported in CP associated with morbid hypothalamic obesity (obesity caused by damage to the hypothalamus **[Au: definition ok?]**)[53, 54, 66-68]. The standardized overall mortality rate varied from 2.88 to 9.28 **[Au: units for these rates?]** in published cohort studies; patients with CP have a 3-fold to 19-fold increased rate of cardiovascular mortality associated with metabolic syndrome when compared with general population[69]. An even higher cardiovascular risk **[Au: rate?]** was observed in female patients with CP **[Au: reasons for this?]**[69].

[H1] Mechanisms/pathophysiology

[Au: In Figure 1 we mention the cell of origin for both ACP and PCP is the remnants of the Rathke's pouch epithelium, but we don't mention this in the mechanisms section. For completeness, please add a short introduction here that explains this embryonic tissue. For example, 'All CPs derive from the remnant epithelium of Rathke's pouch, which is an invagination at the roof of the developing mouth that gives rise to the anterior pituitary gland. In humans, the proliferating anterior pituitary wall does not fill Rathke's pouch, leaving a remnant cleft; it is within this cleft that CPs arise.' I am not sure this statement is correct; there is no cleft in the human pituitary]. That CP derived from RP is mentioned previously in the abstract and the introduction, it is said CPs derived from remnants of the craniopharyngeal duct, which is equivalent to Rathke's pouch. I am not sure we need to repeat it again in this section.

[H2] ACPs

[H3] Tumorigenesis. ACPs are driven by somatic mutations in *CTNNB1* (encoding β-catenin) that are mostly point mutations within exon 3 and that affect regulatory residues involved in β-catenin protein stability[9-11]. The consequence of these mutations is that β-catenin cannot be efficiently degraded, accumulates within the cell and over-activates the WNT/β-catenin pathway, a critical pathway involved in normal physiology and disease including cancer **[Au: which processes are affected?]**[70, 71]. Although multiple studies have reported failure to detect *CTNNB1* exon 3 mutations in a proportion of ACP samples, a finding that may be due to the sequencing approach used and/or a low proportion of tumour tissue within these samples[8, 11, 12], no other recurrently mutated genes have so far been identified. Indeed, ACPs show a low mutational rate with ~15 non-synonymous mutations per megabase[11]. Genomic aberrations, either large losses or gains, are rare in ACPs. In one study, 5 out of 14 ACP tumours showed stable genomes, with recurrent focal losses and gains observed in the remaining 9 tumours analysed; the functional consequences of these findings are unclear[12].

Immunohistochemical studies have revealed the presence of sporadic cells showing nucleocytoplasmic accumulation of β-catenin either as single cells throughout the tumours or in small groups referred to as cell clusters[9, 71, 72] — most of the tumour cells show normal membranous expression of β-catenin despite carrying *CTNNB1* mutations. The reasons underlying this heterogeneity are not known, but it emphasises the notion that not all cells respond equally to the effect of oncogenic *CTNNB1* mutations. These β-catenin-accumulating cells have not been observed in any other tumour of the sellar region, including PCPs[73], and are often located at the base of the finger-like protrusions of tumour epithelium that invade surrounding tissues[74, 75]. **To better understand the mechanisms underlying ACP development, mouse models have been used. [Au: add a linking sentence at the end of this paragraph along the lines of 'To better understand the mechanisms underlying CP development, mouse models have been used.'?]**

Two mouse models that develop tumours that resemble human ACP have confirmed that the *CTNNB1* mutations drive tumourigenesis[71, 76]. In the 'embryonic ACP model', the expression of a degradation-

resistant form of β-catenin (that is, oncogenic β-catenin), leading to enhanced WNT/β-catenin signalling, is targeted **[Au:OK? NO, it is not limited]** to early embryonic precursors of the pituitary gland. By contrast, in the 'inducible ACP model' oncogenic β-catenin is expressed specifically in stem cells that express the transcription factor SOX2 in the murine adult pituitary. Genetic tracing experiments in the inducible model have revealed that normal $SOX2^+$ pituitary stem cells expressing oncogenic β-catenin proliferate transiently and stop dividing to give rise to cell clusters with accumulated β-catenin. Thus, $SOX2^+$ stem cells are the cell-of-origin of the clusters, although SOX2 expression is subsequently lost and only a proportion of the cell clusters express SOX2 by the end of gestation; no $SOX2^+$ cells are detected in human clusters[71, 76-79]. Surprisingly, the tumours of the inducible model do not derive from the $SOX2^+$ stem cells that express oncogenic β-catenin, but rather they develop from $SOX2^-$ cells that are transformed in a paracrine manner by the $SOX2^+$-derived cluster cells[76] (Figure 2A). Paracrine transformation has been previously shown in other neoplasias, such as brain tumours resembling human glioma[80, 81], prostate adenocarcinoma[82], hepatocellular carcinoma and acute myeloid leukaemia[79-81, 83-85]. However, the concept that stem cells can promote tumour initiation in a paracrine manner does not conform with conventional modes in which mutated stem cells become tumour-initiating cells[86, 87]. Of note, when committed or differentiated pituitary cells from embryos or adult mice are targeted with oncogenic β-catenin, tumours do not form, demonstrating that the tumourigenic process requires oncogenic β-catenin to be expressed specifically in embryonic or adult stem cells[71].

Detailed analyses of these murine models have revealed that β-catenin-accumulating cell clusters, as well as single cells with accumulated β-catenin, act as signalling 'hubs' within the tumour. These clusters secrete a plethora of growth factors and cytokines, including sonic hedgehog (SHH), cytokines (such as IL-1 and IL-6) and growth factors (such as SHH, epidermal growth factor, fibroblast growth factor, WNTs, transforming growth factor-β and bone morphogenetic proteins) among others, which activate specific pathways in surrounding nearby tumour cells[8, 78, 88]. This secretory phenotype is compatible with the activation of the pro-tumourigenic senescence-associated secretory phenotype (SASP; see below). The expression of many of these signalling factors and

activation of the pathways have been confirmed in human ACP in several independent studies[8, 88-93]. Further supporting the relevance of paracrine signalling in tumour pathogenesis, it has been shown that cluster cells in both murine and human ACP are molecularly equivalent to the enamel knot, a critical signalling centre during tooth development[8], providing a molecular rationale for the long-observed histological similarities between ACPs, tooth development and dental tumours, as well as a potential explanation for the calcified nature of ACPs[8, 94-96]. Global gene expression analyses of RNA-seq data from isolated murine and human cluster cells have revealed a common odontogenic molecular signature[8, 97].

Recent research has provided insights into the mechanisms underlying paracrine tumourigenesis in ACPs. Gene expression studies in the ACP murine models have shown that cluster cells exhibit the hallmark of cellular senescence: viable but non-proliferative; expression of cell-cycle inhibitors such as p16 (encoded by *CDKN2A*) and p21 (encoded by *CDKN1A*); increased lysosomal compartment (for example, over-expression of senescence-associated β-galactosidase); presence of DNA damage and activation of a DNA damage response; and activation of the SASP[97, 98]. Moreover, studies combining immunohistochemistry with gene expression profiling of laser-captured microdissected clusters have demonstrated that human and mouse clusters share a signature of senescence with activated SASP[8, 97]. To demonstrate that SASP activation underlies the tumour-initiating potential of the cluster cells in the ACP mouse models, the senescence and SASP response was disturbed genetically. These experiments revealed that the attenuation of the senescence and SASP response results in reduced or absent tumourigenesis[98]. In human ACP, the SASP activities of the clusters are likely to act on surrounding epithelial tumour cells to promote proliferation, invasion and an overall pro-tumourigenic microenvironment (Figure 2B) [8, 97].

Together, these mouse and human studies have demonstrated a critical role of senescence in the pathogenesis of ACP. In addition, they provide evidence to support the use of 'senolytics', that is, drugs that are capable of specifically killing senescent cells, in patients with ACP[99, 100]. Anti-senescence therapies are an emerging area of research, with a few drugs already in clinical trials. Thus,

in the near future, clinically approved senolytics are expected to be available for testing in patients with ACP.

[H3] Inflammatory mediators. Numerous cytokines, chemokines and inflammatory mediators are expressed in human CP, in both in the solid and cystic components of ACPs[89, 101, 102 103]. For example, particularly high concentrations of the cytokines IL-6, IL-8, CXCL1 and IL-10 have been reported in the cystic fluid of human ACP[89], findings that have been confirmed and extended in an independent study showing elevated expression of IL-1β, IL-6, IL-8, IL-10, IL-18 and tumour necrosis factor[8]. The receptors and co-receptors for many of these cytokines are also expressed in ACP and active signalling has been demonstrated[89, 91]. Moreover, the pattern of cytokine expression has been shown to be compatible with inflammasome activation, possibly triggered by the cholesterol crystals present in human ACP[8]. Furthermore, the expression of the immunosuppressive factors IL-10, IDO-1 **[Au: do you mean 'indoleamine-pyrrole 2,3-dioxygenase (encoded by *IDO1*)'? YES]** and galectin-1 (encoded by *LGALS1*) are elevated in human ACP, and programmed death ligand 1 (PD-L1) and its receptor PD-1 have been reported in ACP and PCP[104]. These molecules may be promoting escape of immune surveillance by CP[8, 89, 90].

[H2] PCPs

PCPs also exhibit a low mutational rate (15 mutations per megabase). So far, no other recurrent mutations or genomic aberrations have been identified except for somatic *BRAF-V600E* mutations[11, 12]. The expression of oncogenic BRAF-V600E is observed in the majority of the tumour cells of the PCP subtype[11, 93]. BRAF is an upstream regulator of the MAPK pathways, a pathway that regulates many physiological processes and frequently upregulated in cancer. **[Au: ok to add a statement of the general role of BRAF here? If so, please complete]** However, the activation of the MAPK pathway is not observed in all PCP tumour cells, as would be expected, but is restricted to a few tumour cells (namely, the basal cells surrounding the fibrovascular cores, which are structures containing stroma and blood vessels surrounded by a well-defined lining epithelium that supports tumour growth. **[Au: can you define what these cores are? If not here, then in Fig 1 for completeness?]**)[13]. The cells

that demonstrate MAPK pathway activity also express phosphorylated ERK1 and ERK2 (which are signalling molecules downstream of BRAF and main effectors of the MAPK pathway **[Au:OK? NO]**) and SOX2, suggesting that they are undifferentiated precursors **[Au:OK? NO embryonic]**. Interestingly, >90% of the proliferative tumour cells (identified by their expression of Ki-67) are contained within the $SOX2^+$, $pERK1^+/ERK2^+$ cell population, suggesting that the activation of MAPK signalling in $SOX2^+$ cells confers a proliferative advantage and impairs their differentiation potential[13]. This suggests that normal $SOX2^+$ stem cells in the pituitary may be transformed into PCP tumour-initiating cells by *BRAF-V600E* mutation via MAPK activation **[Au: is this what you meant? YES]**.

The causative effect of *BRAF-V600E* mutations has not yet been demonstrated but murine models have revealed interesting insights. For example, the expression of BRAF-V600E in SOX2+ embryonic pituitary progenitor cells results in the expansion $SOX2^+$ stem cells in the developing pituitary, which are bestowed with increased proliferative capacity and impaired differentiation capacity, similar features to the $SOX2^+$ proliferative cell population lining the fibrovascular cores[13]. However, perinatal lethality in this mouse model prevents assessment of the putative tumourigenic effects of these mutant $SOX2^+$ cells, but it is tempting to suggest that BRAF-V600E-expressing $SOX2^+$ cells in human PCP and in this mouse model may be tumour-initiating cells in vivo[13].

The potential role of cell senescence in PCP has not yet characterized, but given that BRAF-V600E is a potent senescence inducer in, for example, melanoma[105], this question merits further investigation. Finally, the expression of inflammatory mediators in PCP has not been investigated, but expression of PD-L1 has recently been described in the basal cells[104].

[H1] Diagnosis, screening and prevention

Patients with CP patients typically present with features of increased intracranial pressure and endocrine abnormalities[106]. Typical work-up should involve a family and patient history, biochemical assessment and a detailed neuroradiological imaging assessment. **[Au: text in green moved up for flow ok?]** Potential differential diagnoses include low-grade gliomas (LGGs), germ cell tumours

(GCTs) and cysts of Rathke's cleft, which are frequently characterized by lower rate of visual impairments, hypothalamic involvement and endocrine deficiencies due to smaller tumour volume **[Au: do you mean smaller lesion volume, as cysts are not tumours?]** at the time of diagnosis[116]. Additionally, secreting pituitary adenomas can be considered, in which symptoms caused by autonomous hormonal hypersecretion are leading clinical manifestations[117, 118].

[H2] Clinical presentation

CP presenting as incidental findings are rare (<2% of all CP cases)[107]. The diagnosis of childhood CP is often made late — frequently years after the initial manifestation of symptoms[106, 108] — with a clinical picture at time of CP diagnosis characterized by non-specific symptoms of increased intracranial pressure (for example, nausea and headache). Further primary manifestations are endocrine deficits (52–87% of patients) and visual impairments (62–84% of patients)[109]. The type and degree of visual impairment depend on the anatomical tumour topography with regard to optic chiasm distortion. Endocrine deficiencies are frequently caused by tumour-related and/or treatment-related disturbances to the hypothalamic–pituitary axis that affect growth hormone (GH) secretion (75% of patients), gonadotropins (namely, luteinizing hormone and follicle stimulating hormone; 40% of patients), thyroid-stimulating hormone (TSH) (25% of patients) and adrenocorticotropic hormone (ACTH; 25% of patients). Endocrine deficits are the first clinical manifestation in the history of 40–87% patients diagnosed with CP, including central diabetes insipidus **[Au:OK?]**, which is observed in 17–27% of patients before diagnosis[110-112]. Pathologically reduced growth rates before diagnosis of CP were observed in patients as young as 12 months of age[108]. Substantial weight gain **[Au: what is substantial, in terms of % or SD increase?]**, predictive of hypothalamic obesity, tends to occur as a later manifestation, shortly before diagnosis of CP. In adult-onset disease, reduced sexual function, due to hypothalamic–pituitary gonadotropin deficiency and hyperprolactinaemia, is a major symptom[113, 114], which is not observed in the paediatric population due to prepubertal status. Additionally, typical symptoms of adult-onset PCPs are high intracranial pressure and hypothalamic symptoms, including psychiatric alterations[115].

[Au: text in green moved up for flow] Studies on history before diagnosis and the prognostic relevance of duration of history and specific clinical manifestations are thus far confined to the paediatric age group; data for adult-onset patients have not been published. For example, a positive correlation has been reported between patient age at diagnosis and duration of history, whereas tumour size, degree of resection, hypothalamic involvement and body mass index (BMI) at diagnosis were not associated with duration of history[106]. Shorter duration of history was observed in patients with CP presenting with hydrocephalus (accumulation of cerebrospinal fluid (CSF) within the brain **[Au: definition OK?]**) at diagnosis. Patients presenting with endocrine deficits at CP diagnosis had a longer duration of history, whereas functional capacity and progression-free survival rates were not associated with specific symptoms in history[106]. Even though hypothalamic obesity is a frequent sequelae in childhood-onset ACP[119], diencephalic syndrome leading to severe weight loss and cachexia can also occur as a rare (4.3% of 485 patients recruited in the German Childhood Craniopharyngioma Registry) hypothalamic disturbance of body composition in childhood-onset CP[120, 121]. However, diencephalic syndrome at the time of CP diagnosis does not preclude weight gain during follow-up[121].

[Au: deleted the final paragraph as it repeated what has already been stated above]

[H2] Neuroradiological characteristics

[H3] CPs. On MRI without contrast, the solid parts (including calcific tissue) and cyst walls of CPs, and ACPs in particular, may show a variety of T1-signals from hypointense to hyperintense[123] (Figure 3A). On T2-weighted images, the tumours are usually hypointense and hyperintense owing to the inhomogeneous distribution of calcifications and the broad individual variation of the MRI signal of calcifications (Figure 3B). Accordingly, confirming the presence or absence of calcifications is usually not possible by MRI in CPs. Moreover, the ideal sequences for the identification of calcifications are T2*-weighted or susceptibility-weighted sequences, which are both hampered by the air content of the sinuses in the central skull base. The proof of calcifications on imaging is also important for the differential diagnosis to other tumours in the sellar **[Au: intrasellar?]** and suprasellar region.

Accordingly, despite the desire to avoid use of X-rays in children, CT is the gold standard for the identification of calcifications in this area (Figure 3C).

[Au: new paragraph] Even if the postoperative MRI does not show a suspicion of a residual tumour, a residual calcification may remain undetected by MRI. The guidelines for imaging in the ongoing CP study **[Au: which study?]** advise performing a postoperative, unenhanced CT only of the tumour region and avoiding the eye lenses. Such a CT should reveal a persisting calcification that the postoperative MRI failed to detect, with the assumption that a residual calcification indicates a residual tumour **[Au: is this what you meant?]**. However, small residual calcifications (<2 mm in size) do not necessarily lead to an increased rate of relapse compared with postoperative sites without residual calcifications[124]. In our experience **[Au: all authors? If just certain authors, please include their initials in brackets here]**, CTs are not performed routinely to avoid irradiation in paediatric patients. However, one patient in our care had a tiny calcification (xx mm in size **[Au: size?]**), which was not detectable on postoperative MRI; after some months the patient experienced a relapse around the tiny calcification (Figure 3 D, E, F)[15]. Thus, xxx **[Au: what is the implication? That postop CT should be more routine despite the potential risk of irradiating patients that don't have calcifications?]** **[Au: merged paragraphs]** Additionally, the CP **[Au: ACP?]** cysts may contain material with a high **[Au: hyperintense?]** signal on T1-weighted MRI. The cysts are filled with an oily fluid (colloid) that is typically secreted by the tumour epithelium and, therefore, also highly diagnostic for an ACP[125] (Figure 3G).

By contrast, **[Au:OK?]** the imaging-based diagnosis of PCP is made by virtue of the fact that PCPs are mostly solid or combined solid-cystic round tumours, rarely contain calcifications, usually lack colloid-filled cysts and occur mostly adults[128].

[Au: new paragraph. Text in green moved down for flow ok?] Additionally, typical imaging characteristics have been reported in CPs harbouring specific mutations[126, 127]. For example… **[Au: can you give a couple of examples for completeness?]** There are only few reports in the literature on

spinal metastasis of CP[129] (Figure 3H) **[Au: rearranged fig 3 panels so they are referenced in order ok?]** and on primary ectopic CPs most frequently observed at the cerebellopontine angle location[6] (Figure 3I **[Au: please provide an image of this; the original image corresponding to this panel was of a recurrence in the right pterional surgical access site, which I've now removed]**). **[Au: the implication being, therefore, that they are difficult to diagnose on imaging? Please clarify]**

An accurate preoperative MRI assessment is important to predict the exact tumour topography[130] and the type of tumour adherence to the hypothalamus[131]. **[Au: can you briefly state why topography and type of adherence are important to know? Do, for example, ACP and PCP show different patterns? Are these of prognostic significance?]** Assessment of seven fundamental MRI variables can fulfil this goal: extent of third ventricle occupation by the tumour, **[Au: degree of?]** pituitary stalk distortion, relative position of the hypothalamus in relation to the tumour, extent of chiasmatic cistern occupation, the mammillary body angle, the type of chiasm distortion and the tumour shape. A position of the hypothalamus around the middle portion of the tumour, a pituitary stalk amputated by the lesion and an elliptical or multilobulated tumour shape are strong predictors of the infundibulo-tuberal and secondarily intraventricular topographies, which are characterized by strong and extensive CP adhesions to the hypothalamus.

[H3] Low-grade gliomas and germ cell tumours. The main differential diagnoses in the intrasellar and suprasellar area in children are low-grade gliomas (LGGs) (Figure 3J), in particular hypothalamic–chiasmatic gliomas, and germ cell tumours (GCTs) (Figure 3K). The peak age of incidence overlaps with that for CPs; for hypothalamic–chiasmatic gliomas, the peak age is ~5 years with both sexes being affected approximately equally[132]. GCTs (most frequently germinomas) have their peak incidence in the second decade of life but can also affect young adults; there is a strong male preponderance[133].

[Au: new paragraph] LGGs are mainly solid, can contain large cysts in the suprasellar region, have a very high **[Au: hyperintense?]** T2- **[Au: weighted?]** signal and increased diffusivity (seen as a bright

signal on apparent diffusion coefficient images). LGGs are usually hypodense or isodense on CT[134]. In the absence of histological analysis and if the cell density of a suprasellar lesion is unclear, an unenhanced CT has been proposed as an additional means to confirm the diagnosis of an LGG; CT can assess the cell density of a tumour provided that there are no calcifications[135]. Interestingly, very large LGGs in the suprasellar region — also called supratentorial midline gliomas — are not accompanied by an impairment of the pituitary gland on imaging[136]. The physiological hyperintense signal of the posterior pituitary gland (the so-called bright spot on unenhanced T1-weighted MRI, representing oxytocin secreting granula in the gland) is usually visible in LGGs, in contrast to CPs in which the hyperintense signal of the posterior pituitary gland may be preserved or missing and not obviously linked to the individual tumour size or localization[15].

GCTs, especially the non-secreting variant, are also mainly solid. Secreting GCTs, which are usually more inhomogeneous **[Au: in what sense?]** compared to non-secreting germ cell tumours, may show more or larger cysts[137]. GCTs contain areas of isointense or low T2 **[Au: weighted?]** signals[138] similar to CPs. The density of a GCT or CP is visibly higher on CT than the density of LGGs. GCTs and CPs are also frequently associated with an atrophic pituitary gland on imaging. The physiological hyperintense signal of the posterior pituitary gland on unenhanced T1-weighted MRI is usually absent in GCTs[15, 139].

[H3] Other sellar and parasellar lesions. Another important differential diagnosis for CPs are cysts of Rathke's cleft, which are small purely cystic lesions in the intrasellar and/or suprasellar area (Figure 3L). These tumours may be indistinguishable from small purely cystic CPs. Another non-tumorous lesion in this area is the xanthogranuloma, which is a potentially post-inflammatory lesion that is, consequently, not included in the WHO classification of brain tumours. Xanthogranulomas may be found in other parts of the brain, skull base or body and contain blood degradation products such as methemoglobin (rendering the T1-signal high **[Au: rendering the T1-weighted signal hyperintense?]**), which is a diagnostic hallmark. However, colloid in small CPs has the same imaging characteristics on MRI; accordingly, small colloid-containing CPs may be indistinguishable from

xanthogranulomas. A Japanese group has reported that the absence of calcification is a possible means of differentiating xanthogranulomas from CPs[140]. Conversely, other reports could not confirm this observation[116], casting doubt on the usefulness of calcifications in the differential diagnosis **[Au: edits for flow ok?]**.

Another differential diagnosis, pituitary adenomas, are uncommon lesions in childhood. The peak age for microadenomas of the adenohypophysis (diameter <10 mm) is 20–50 years of age; for macroadenomas (diameter >10 mm), the peak age is 20–40 years. The main diagnostic clue **[Au: that distinguishes these lesions from CPs?]** in macroadenomas is the missing separate identification of the pituitary gland owing to the mass being the adenoma of the gland. Larger adenomas **[Au: Macroadenomas?]** not only extend **[Au: 'extend through'?]** the sellar diaphragm superiorly but often result in a snowman-like appearance of the mass caused by a tallying **[Au: 'constriction' instead of tallying?]** of the mass at the level **[Au: 'opening' instead of 'level'?]** of the sellar diaphragm. Enhancement is variable and cannot predict the type of secretion of the adenoma. **[Au: for brevity, I suggest removing the statements in green; please consider this suggestion. If not, please address the queries]** However, enhancement usually enables delineation of the adenoma **[Au: what do you mean by delineation here? Is it confirmation of the type of adenoma or confirmation that a given lesion is an adenoma?]**. An infiltration **[Au: by a pituitary adenoma?]** of the cavernous sinus and the skull base is possible. Pituitary hyperplasia with an upward convex border of the gland is regularly present in 25–50% of females between 18–35 years of age **[Au: what is the implication of this?]**. In end organ failures, for example of the gonads or the thyroid gland, a reversible pituitary hyperplasia may develop[141]**[Au: what is the implication of this?]**. In microadenomas of the pituitary gland, the clue to diagnosis is one feature or a combination of the three following characteristics: a lowering of the floor of the sella on the respective side, a lifting of the upper border of the gland on the respective side or a 'sidestep' displacement of the pituitary stalk to the other side of the gland. Usually, microadenomas take up contrast media less than the normal pituitary gland and are, therefore, better detectable on post-contrast MRI[142, 143].

Other tumours arising from the pituitary gland like pituicytomas are either extremely rare or affect mainly adults and, therefore, not included in the differential diagnosis.

[H2] Hypothalamic involvement

Once identified, determining the potential treatment approach and/or sequelae of a CP and its resection requires knowledge of the tumour size and localization[130]. In normal anatomy, the nuclei of the posterior hypothalamus are localized in the lateral walls of the third ventricle, beginning at the level of the mammillary bodies and posterior to them[146]. As the mammillary bodies are easily identifiable on normal axial and thin sagittal slices on MRI, they provide useful reference points. **[Au: sentence in green added for flow ok?]** From these reference points, different scales have been developed to define tumour size and location preoperatively. **[Au: next two sentences moved down for flow ok?]** For example, the German KRANIOPHARYNGEOM 2000/2007 studies used a classification of CPs according to their contact or compression of different structures of the hypothalamus[116, 145]. In another example, Puget *et al.*[144] used preoperative MRIs to define hypothalamic involvement with aim of avoiding further damage during resection; three grades were defined **[Au:OK?]**. Grade 0 CPs have no contact with the floor of the third ventricle (Figure 4A). Grade 1 CPs have contact with or compress the hypothalamus anterior to the mammillary bodies (Figure 4B). Grade 2 CPs are those resulting in a dislocation, compression or destruction of the hypothalamus, beginning at the level of the mammillary bodies or dorsal of **[Au: to?]** them (Figure 4C)[116, 145].

Some have emphasised that even if the grading described by Puget *et al.*[144] intuitively makes sense, a reliance on subjective criteria for the differentiation between grade 1 and 2 is a limitation[147]. For example, a CP with a voluminous cyst in the sellar space may hide a little calcified or solid area within the infundibulum and may be incorrectly classified as grade 0. Once the cyst is removed, the grade may be refined to grade 1 as there is a slight involvement of the anterior hypothalamus but the remaining hypothalamus is intact. However, some CPs of the same origin may expand within the hypothalamus itself[148], and will be defined as grade 2 (Ref[144]). Accordingly, classification in three grades seems to require further clarification. **[Au: is this what you meant?]**

[H2] Prognosis

[Au: Can you begin this section with a brief statement introducing the factors that may be associated with prognosis? Number of interventions, BMI, histology, etc.] The association of outcome after CP with the frequency of neurosurgical operations is difficult to interpret owing to the cofounding factor that repeated procedures are necessary in case of relapse and progression, which have additional impact on prognosis and QOL. For example, patients with childhood-onset CP who developed severe obesity (BMI ≥7 standard deviations **[Au:OK?]**) due to hypothalamic syndrome received more surgical interventions (mean 1.74; range 1–4) and showed lower functional capacity, when compared with normal-weight patients (mean number of surgical interventions1.39; range 1–5)[149].

The prognostic relevance of histological tumour type is controversial. Better 5-year overall survival rates have been reported in PCP than in ACP and in tumours of combined histological types[59, 60]. In adult-onset ACP, increased perioperative mortality has been described **[Au: compared with PCP?]**, but other reports could not confirm these prognostic differences between both histological subtypes **[Au: reference?]**. No specific histopathological feature can thus far predict survival after childhood-onset CP. In an adult-onset CP cohort, CPs lacking calcifications have been described to be associated with more favourable prognoses **[Au: does this reflect chance of recurrence with postop calcifications as mentioned in the previous section?]**[150]. Whether initial hydrocephalus has prognostic impact is also still a matter of debate. Increased mortality rates due to primary hydrocephalus and increased intracranial pressure at the time of diagnosis has been described, as well as a lack of association between initial hydrocephalus and mortality[55, 151].

[Au: moved the text in green down for flow ok?] With regard to prognostic impact of hypothalamic integrity, Elowe-Gruau *et al.*[24] demonstrated in their retrospective study **[Au:OK?]** that a hypothalamus-sparing surgical treatment strategy increased the rate of 'normal' long-term BMI from 17% to 38% compared with GTR **[Au:OK?]**. However, the percentage of clinically relevant weight

546 gain remained 62% **[Au: do you mean that the average weight gain was a 62% increase? Or that**
547 **of those who gained weight, it was a 62% increase? For which arms of the study?]** with ~50% of
548 all patients **[Au: regardless of surgical intervention?]** developing morbid obesity **[Au: defined as?]**
549 during follow-up **[Au: which was how long?]**. Furthermore, the mean number of surgical
550 interventions per patient, used as a surrogate for the local recurrence rate, was not noticeably different
551 between the two groups (1.52 in the hypothalamus-sparing strategy group versus 1.45 in the GTR
552 group). However, follow-up was markedly shorter in the GTR group (mean, 33 months) when
553 compared with the historical group treated by GTR (mean, 103 months) **[Au: it's unclear why we're**
554 **comparing to a historical group, when the trial was between hypothalamus-sparing vs GTR;**
555 **please clarify or consider removing this statement for simplification]**. Validation of these
556 observations in a prospective multicentre setting is still missing. In another report, 20-year overall
557 survival was shown to be reduced in patients with CP with hypothalamic involvement[152]. However,
558 the authors found that 20-year progression free survival rates were not associated with the degree of
559 surgical resection and not related with the adjuvant use of radiotherapy, supporting the notion that
560 GTR has no advantage in terms of preventing CP recurrence.
561
562 **[H1] Management**
563 **[Au: in the Introduction you mention antibiotics and corticosteroids have improved treatment,**
564 **but these are not mentioned in the Management section; please make mention of these for clarity**
565 **and completeness. Presumably they are given at the time of surgery to reduce infection risk and**
566 **inflammation, but this should be stated explicitly in the surgery section]** The best treatment for CP
567 is the one that leads to the least long-term morbidity. Treatment may include surgery alone, irradiation
568 alone or, more commonly, a combination of the two. Surgery alone implies GTR **[Au:OK?]** and is,
569 therefore, appropriate for tumours that may be completely resected without neurovascular injury and
570 visual impairment. Surgical management, especially in children, remains controversial and ideally
571 must be carefully planned **[Au:OK?]** (Box 1). Of note, treatment of CPs varies in different parts of the
572 world (Box 2). A major factor that affects patients with ACPs is hypothalamic dysfunction with
573 associated obesity. In the paediatric population, preoperative hypothalamic involvement (Figure 4)

increases the likelihood of preoperative and postoperative obesity, and hypothalamic damage during surgery increases the risk of postoperative weight gain[24, 144, 153, 154]. Although less well established, postoperative weight gain in adults is also a problem and correlates with hypothalamic involvement[147, 155]. Accordingly, avoiding irreversible hypothalamic damage is a key goal in treatment of CP. **[Au: please include a statement about how treatments may vary based on whether the CP is ACP or PCP. Also, this section mainly describes ACPs, so we need to explain the choice – the evidence base is greater, frequency is more? Just for clarity. For example 'Here we primarily discuss options available for ACP, owing to the great evidence base, number of patients and global experience. Some principles of care can be translated to patients with PCP…']**

[H2] Intracystic therapies

Intracystic treatments are an alternative option to surgical resection in well-selected patients with pure or mainly monocystic CP **[Au: ACPs?]**. Particularly useful in the youngest patients, intracystic therapies can assist in postponing radiotherapy and should be performed by experienced multidisciplinary teams only. Intracystic treatment with interferon-α (IFNα) provides the best benefit to risk ratio, but is limited to the cystic portion, with no effect on the solid component of the tumour. A recent international review of 55 children showed progression in 42 patients with IFNα treatment after a median time of 14 months[156].

[Au: new paragraph] Additionally, radiotherapy agents (^{90}Yttrium and ^{32}Phosphorus) or chemotherapy (bleomycin) can be used intracystically, but these agents may be associated with irreversible neurotoxicity or even death and have not proven to be consistently efficacious. Indeed, in a recent review, the available evidence could not support the use of intracystic bleomycin in children on the basis of benefits and harmful effects[157]. Thus far, studies on intracystic therapies are small, underpowered and limited data can support the use of intracystic therapies.

[H2] Emergency surgery

Raised intracranial pressure and/or vision loss are indications for urgent surgical decompression. In such cases, the signs are often reflect biventricular hydrocephalus due to the tumour in the third ventricle. In case of cystic components at this level, the problem can be corrected by placing an intracystic catheter and, later, an ommaya reservoir (an implanted intraventricular catheter device **[Au:OK?]**) to enable repeated aspiration of the cystic fluid **[Au: colloid?]** or to deliver intracystic therapy[156, 157]. The catheter can be placed during an open surgery (rare), a stereotactic procedure or, preferably, an endoscopic approach and can offer a good option to postpone a more aggressive surgery or radiotherapy[158]. In case of hydrocephalus, a shunt should be avoided as a first option as it may lead to slit ventricles in some cases and can complicate a **[Au: subsequent?]** surgery with a ventricular approach. In case of optic chiasm compression with visual loss by a solid or calcified component or tumour bulk obstructing the third ventricle, a direct surgical approach is the only possible option.

[Au: moved the text on PCP treatment to the end for flow]

[H2] Planned surgical resection

Risk-adapted treatment with grading systems have been proposed and evaluated to prognosticate postoperative weight gain and, therefore, to adapt the best surgical strategy to spare the hypothalamus as much as possible[23, 24, 144, 161, 162]. Additionally, a careful examination of the preoperative MRI for other anatomical hallmarks is important to identify the length of the optic nerve pathways, the location of the anterior communicant artery (that corresponds to the location of the optic chiasm), the sellar diaphragm (well defined on sagittal and coronal T2 **[Au: weighted?]** MRI), the size of the ventricles, the presence of a septum pellucidum (a membrane separating the anterior horns of the left and right lateral ventricles **[Au: definition ok?]**), the hypothalamic structures (the floor of the third ventricle and the mammillary bodies are well defined on on sagittal T2**[Au: weighted?]** MRI), and the angle between the mammillary bodies and the brainstem in case of hypothalamic involvement[148, 163, 164], which is particularly important for grade 2 tumours to evaluate the displacement of the hypothalamus and to choose the best surgical route (Figure 4). **[Au: text in green paraphrased from the original for brevity; please check carefully]** Another important aspect to determine is adhesion of the tumour to the hypothalamus, which if resected could worsen the hypothalamic damage. A comprehensive

categorization of CP adhesion has been proposed[160]; CPs associated with the worst outcome were those that had an hypothalamic adhesion (to the third ventricle floor and its walls). **[Au: following sentence added for flow ok?]** The aforementioned preoperative grading system to define hypothalamic involvement[144] is essential when planning a surgical strategy.

[H3] Grade 0 hypothalamic involvement. **[Au: subhead added ok?]** In grade 0 CPs, there is no hypothalamus involvement, and most tumours occupy the subdiaphragmatic space[144]. An EEA is ideal in these cases and is commonly used in adult patients with CP **[Au: ACP?]**. In children, this technique, in which the tumour is removed through the nasal cavity **[Au:OK?]**, has increased its indications owing to the progress in reconstructive surgery whereby use of a nasoseptal flap decreases the occurrence of CSF leak[110, 165]. The use of neuronavigation (that is, computer-assisted technologies to guide the surgeon within the confines of the skull **[Au: definition ok?]**) has overcome the problems of non-pneumatized **[Au: 'arrested pneumatized'?]** sphenoid sinus (in which… **[Au: individuals have a persistent atypical fatty marrow adjacent to the sinus'? description needed for completeness]**) or a short intercarotid distance[166, 167].

[H3] Grade 1 hypothalamic involvement. **[Au: subhead added ok?]** In grade 1 CPs, the tumour pushes or compresses the hypothalamus (identified by preoperative MRI) because the lesion has either developed at the levels of the infundibulum or pituitary stalk and extended in the sella turcica or developed entirely in the third ventricle. In some cases, GTR can be performed if there is a plan **[Au: plane?]** of dissection from the floor of the third ventricle, provided the neurosurgeon is skilled and the CP topology allows it[144]. A transcranial route has been used traditionally, assisted when necessary by endoscopy to reach blind spots; however, an EEA is also a good option — especially if the lesion is strictly subdiaphragmatic[110]. For tumour that develop in the third ventricle, a transcranial approach is recommended, especially in children[110, 165].

[H3] Grade 2 hypothalamic involvement. **[Au: subhead added ok?]** In grade 2 CPs, the hypothalamic structures cannot be clearly identified due to invasion of the tumour. Grade 2 tumours

represent 40–70% of CPs **[Au: or specifically ACPs?]** in different series[144, 168-170]. The most frequent transcranial routes are transcallosal, frontal transcortical, pterional and unilateral or bilateral subfrontal approaches[165, 171-173], and contemporary options are increasingly precise techniques. To make surgery safer and more accurate, the approach taken is selected according to the position of the hypothalamus, which can be determined on sagittal MRI (showing either upward or downward displacement of the mammillary bodies and the upper brainstem)[146]. During surgical planning, the surgeon must anticipate the maximal safe resection of the lesion either in one or several stages[110, 144, 172]. If several stages are needed **[Au:OK?]**, the impact of the first surgery must be anticipated on the CSF cavities and pathways, and the displacement of the residual lesion. The EEA is not recommended for grade 2 tumours, except in some rare cases, because it is very difficult to safely preserve invaded hypothalamic structures[172]; however, crossing the involved third ventricle floor seems less deleterious in adults than in children[19, 174]. The limits of EEA for third ventricle CP have been recently reported[165, 172, 175]. However, endoscopy can be used in combination with microsurgery to look 'around the corners' and maximize safe resection.

[H3] Post-operative hypothalamic damage. **[Au: subhead ok?]** In terms of assessing post-operative hypothalamic damage, which is **[Au: frequently?]** inevitable given the anatomical location of most of these tumours, De Vile *et al.*[176] have defined a classification of the extent of the postoperative hypothalamic damage. Divided into three grades, the system characterizes the severity of the damage depending on the postoperative abnormalities and defects in the floor of the third ventricle (Figure 5). The rate of severe postoperative obesity is associated with the grade of hypothalamic damage[176]. Further outcome parameters such as QOL or neuroendocrine deficiencies were not assessed in the report by De Vile *et al.*[176] Several extended classifications have subsequently been published, all confirming the observed association between outcome and grade of hypothalamic damage[116, 145, 147, 153, 162, 177-180]. Finally, after any surgery, cell nests might be displaced from the original tumour site into the tract of access and implantation, 'metastases' may rarely be the consequence[181].

[H2] Radiotherapy

[Au: Although the referees asked for expanded discussion on RT, the section was far longer than needed; I have tried to reduce length – please check carefully] Surgery alone may not be appropriate for tumours that have invaded **[Au:OK?]** the hypothalamus[148]. Instead, radiotherapy — typically with external beam radiotherapy using photons or protons[182] — can be used alone or in combination with limited surgery. **[Au: sentence in green moved up for flow]** The appropriateness of limited surgery and radiotherapy depends at least in part on the tumour extent and other characteristics[26]. Radiotherapy can also be delivered at the time of progression after prior surgery or as part of planned limited surgery and radiotherapy approach. **[Au: moved the rest of this paragraph up from later in the section for flow:]** Tumour control rates after radiotherapy with limited or no surgery are similar to control rates of GTR or subtotal resection **[Au: which is?]** with radiotherapy, with a >90% 10-year overall survival estimated from US Surveillance, Epidemiology, and End Results (SEER) data[183]. However, the SEER data analysis did not match functional outcomes to treatment or include a large proportion of children treated with definitive radiotherapy. In children, radiotherapy choice must be carefully weighed given the potential adverse effects (Box 3). **[Au: to save space, and mirror the similar box on surgery, I moved the discussion of RT effects to a box ok?]**

Limited surgery and radiotherapy involves surgery to alleviate and prevent symptoms (for example, to reduce visual impairment and mass effect on the brain), improve the patient's ability to tolerate and complete irradiation, and potentially enhance or optimize dose delivery; it is appropriate for most patients **[Au: regardless of age and tumour type?]**. Limited surgery includes partial resection, cyst fenestration or aspiration (although the fluid may reaccumulate), catheter and ommaya reservoir placement, or CSF diversion (to restore CSF flow **[Au:OK?]**). Limited surgery also reduces the tumour volume for irradiation and the radiation dose delivered to critical normal tissue, but diabetes insipidus should be considered an unanticipated complication. The extent of resection can be minimized to the amount required to achieve the goals of the procedure because the amount of residual tumour has not been shown to influence tumour control after radiotherapy[183].

[Au: this paragraph in particular was heavily edited for brevity; please check carefully] The planning of radiotherapy (using protons or photons) requires the engineering of customized immobilization devices to reproducibly position the patient at each session, CT with or without contrast media to calculate the radiation matrix and as a reference for daily set-up, and (ideally) MRI to serve as a baseline for the cystic and solid tumour. Depending on the modality used, the postoperative residual tumour and/or tumour bed is contoured to form the target volume with margins to account for geometrical variability in patient set-up or other intra-fractional uncertainties. Beam directions and orientation depend on the planning type and treatment modality. **[Au: merged paragraph]** Conventional radiotherapy uses X-rays directed from multiple directions to conform the prescription dose to the target volume while sparing non-target tissue, which receive collateral dose associated with the entrance and exit of the traversing beams. By contrast, proton beam therapy deploys fewer beams that deposit dose along a path that ends in the target; the dose to non-target tissue is significantly reduced. Regardless of modality, the hypothalamic–pituitary axis, optic nerves and chiasm, the principle components of cerebral circulation, and portions of the brainstem receive the prescription dose in most cases. However, patients, and their parents and caregivers, often prefer the proton beam modality[147] based on the hope that the difference in normal tissue doses will provide an advantage in terms of adverse effects.

Indeed, preliminary reports of first-generation proton beam therapy (passive scatter) suggested that the rate and pattern of failure, and rates of necrosis, vasculopathy and severe neurological complications, were equivalent to photon therapy[184]. Preliminary results also suggested that when corrected for the distribution of radiation dose in normal brain, those treated with proton therapy had no change in academic achievement scores (reading and math) compared with patients treated with photon therapy, who showed a significant decline[185]. Since 2016, a newer generation of proton therapy (pencil-beam scanning) has become available. The advantage of this method is the use of small, individually-weighted beams to further conform to the prescription dose to the target and reduce the volume that receives the highest doses.

As the precision of radiotherapy increases, a plateau in our ability to reduce dose to normal tissues will not be achieved unless consideration is given to lowering the total dose of irradiation, which is generally 50–54CGE administered in divided doses 5 days per week over 6 weeks. Designing a trial to appropriately reduce or escalate radiation dose in CP is made difficult by the limited number of patients and even smaller number of events after irradiation.

[Au: moved this section on PCP treatment to the end as the previous text largely focused on ACPs ok?]

[H2] PCPs [Au:OK?]

Although they represent only 10% of all CPs (with <25 cases described in the paediatric population[159]), the papillary-squamous type **[Au: PCP subtype?]** harbours a few specificities compared to their ACP counterparts, which may influence the surgical technique. In a retrospective study surgical data of 500 CPs, the squamous-papillary variant **[Au: PCP subtype?]** typically presented as a solid mass with no or rare calcifications, had more 'loose' adhesions and predominantly a sessile or pedicle attachment (63%) in the inner lining of the third ventricle of the brain, compared with ACPs, which was associated with the widest and strongest adherence[160]. PCPs are rare tumours, with less adherence to the hypothalamic structures compared to the ACPs, which could in theory favour better and safer GTR. **[Au: Please discuss a little more in detail treatment options for PCPs. For example, can EEA approach work? Radio/surgical combination? Radiotherapy alone? If there are no studies/data/etc please state so for completness]** Moreover, the vast majority of them harbour the *BRAF-V600E* targetable mutation, which offers hope for treatment of this subtype.

[H1] Quality of life

[Au: given how well this section described the QOL elements, I opted to remove the box, but moved the text in green up into the main text.] Functional and social independence is the goal of the survivor, their family and treatment team. Systematic analysis of long-term health-related quality of life (QOL) has not yet been established in patients with craniopharyngioma (CP). Eveslage *et al.*[235]

reported on short-term QOL during the first 3 years after CP diagnosis in patients recruited in the multinational trial KRANIOPHARYNGEOM 2007 trial[251]. Patients with CP who were treated with radical surgical strategies such as gross total resection (GTR) that resulted in surgical lesions of posterior hypothalamic areas presented with significant lower self-assessed and parental-assessed QOL. **[Au: which domains of QOL were assessed in this report?]**

Most of the complications of CP and its treatment, including some that are irreversible, can be managed with medicine and psychological, emotional and spiritual care. First and foremost are life-threatening endocrine deficiencies that require daily replacement therapy: central hypothyroidism, central adrenal insufficiency and central **[Au:OK?]** diabetes insipidus. Medical treatment of excessive daytime sleepiness, narcolepsy and attention disorders; interventions designed to improve cognition; and individualized plans for education and work comprise a list of evaluations and treatments that need to be undertaken early with patients to help them achieve normalcy. Finally, attention to insidious problems that may arise after treatment, such as vasculopathy, requires regular surveillance and secondary prevention when warranted, including cerebral angiography and revascularization[62]. Interventions should be broadly implemented **[Au: what do you mean by broadly implemented? That each patient will require this type of care?]** for these patients, who often present with weak neurocognitive performance and overall condition[186].

[H2] Endocrine deficiencies

Endocrine deficiencies of hypothalamic–pituitary axis result in the necessity of life-long hormonal substitution. At least three pituitary hormone deficiencies have been reported in 54–100% of patients[187,188]; postoperative ACTH deficiency occurs in 55–88% of patients, GH in 88–100% of patients, TSH in 39–95% of patients, gonadotropins in 80–95% of patients and arginine vasopressin in 25–86% of patients **[Au:OK?]**. In case of insufficient hormone substitution, severe adverse effects such as short stature (for GH deficiency) or life-threatening emergency situations such as adrenal crisis leading to dramatic reductions in cortisol levels **[Au:OK?]** (for ACTH deficiency) are common[152].

Substitution therapy with recombinant GH is safe with regard to risks of tumour progression and recurrence[189]. QOL seemed to be stabilized in GH-treated patients with CP during short-term follow-up of 3 years, whereas beneficial GH effects on the development of hypothalamic obesity were not observed during the first 3 years after diagnosis[190]. During long-term follow-up (assessed >12 years after diagnosis), patients with CP who were treated with GH during childhood showed better QOL, height and weight development, when compared with CP patients in whom GH substitution was initiated at adulthood[191]. Endocrine substitution of deficient hypothalamic–pituitary axes for TSH, gonadotropins and ACTH is safe and efficient **[Au: in terms of cancer recurrence, QOL, and correcting the endocrine deficiency? Please clarify, and cite appropriate references for each hormone type after each is listed in this sentence]**.

[H2] Hypothalamic obesity

[H3] Pharmacological treatment. Due to impairments in satiety regulation, energy expenditure and central sympathetic output, patients with CP who have hypothalamic syndrome typically develop morbid obesity. These patients may also have so-called parasympathetic predominance due to vagal activation, which manifests with reduced body temperature, reduced heart rate and increased daytime sleepiness[192]. Importantly, the obesity is usually unresponsive to conventional treatment efforts such as lifestyle modifications[193] and may, therefore, require pharmacological intervention. **[Au: edited for brevity; references in the table do not need to be cited here as well]** The approaches to date have included stimulants such as amphetamine derivatives, methylphenidate to increase physical activity and agents that modulate insulin sensitivity amongst others (Table 1). However, none of these approaches has been proven to be effective in controlled randomized trials in patients with childhood-onset CP and hypothalamic obesity[202].

Another pharmacological target is oxytocin, a hypothalamic hormone that suppresses appetite under normal conditions; loss of oxytocin neurons may be involved in hypothalamic obesity in patients with surgical damage limited to specific anterior hypothalamic structures[203] **[Au: introduction added to explain oxytocin ok? Please edit as necessary]**. **[Au: edited for brevity ok?]** Accordingly, oxytocin

substitution was hypothesized to have beneficial effects on neurobehavioral deficits in these patients. A small pilot study (*n*=11) showed that a single nasal application of oxytocin[204] was well-tolerated and increased oxytocin concentrations in saliva and urine. The patients showed improvements with regard to emotional identification compared with patients with anterior and posterior hypothalamic lesions. In another analysis, CP with anterior hypothalamic lesions and CP with anterior and posterior hypothalamic lesions presented with distinct patterns of eating behaviour in terms of hunger level, eating style and bulimia[205]. Our current knowledge on the long-term effects of oxytocin treatment in CP is mainly based on a few case reports. Parental-observed oxytocin treatment improved prosocial behaviour in a paediatric case[206], and improved hyperphagia and weight loss in combination with naltrexone in another case[207].

[H3] Bariatric treatment. **[Au: sentence in green moved up for flow]** Individualized treatment approaches based on assessment of clinical domains such as eating behaviour affected by hypothalamic syndrome has been recommended[212]. Short-term BMI reduction with bariatric surgery has been reported in studies analysing 5–10 years follow-up data in patients with childhood-onset CP with hypothalamic obesity[208, 209]. Clinically significant improvement of binge-eating behaviour was observed immediately after laparoscopic adjustable gastric banding (LAGB) these patients[208]; LAGB was well tolerated, but long-term **[Au: after how long?]** weight reduction was not achieved[210]. A meta-analysis **[Au: encompassing how many patients?]** reported that at 12 months post-procedure, Roux Y gastric bypass, biliopancreatic diversion and sleeve gastrectomy were the most efficient bariatric treatment of childhood-onset CP with hypothalamic obesity[211]. Bariatric treatment with non-reversible surgical techniques is controversial in the paediatric age cohort owing to legal, medical and ethical concerns[210]. Currently no bariatric treatment method has been proven to be efficacious in randomized controlled trials in patients with CP with hypothalamic obesity[213].

[H2] Neuropsychosocial functioning **[Au: we have a character limit of 40; is this edit from 'Neuropsychological and psychosocial functioning' ok?]**

Studies assessing physical and psychosocial functionality during long-term follow-up after CP report variable observations, ranging from reduced function in ~50% of patients to excellent function in the majority of patients[53, 214-216]. Reductions of social and emotional functioning are the most frequently observed impairments, with patients rating their psychosocial status to be worse than their physical health[53]. Other complaints are somatic symptoms such as reduced mobility and pain[53]. Behavioral studies observed frequent psychopathological symptoms, such as anxiety, depression and withdrawal; recently, increased risk of apathy in long-term survivors of childhood-onset CP was reported[217]. Difficulties in learning, emotional control, concerns with regard to physical appearance and body image, and unsatisfactory peer relationships are frequent problems in children's daily functioning[218, 219].

Younger age at diagnosis and pre-surgical functional impairments are known risk factors associated with reduced psychosocial and neurocognitive function after treatment **[Au:OK?]**. Endocrine, ophthalmological and neurological side effects adversely affect neuropsychological outcome after CP[53, 214]. Hypothalamic dysfunction is the most clinically relevant negative risk factor for impairments in body image, social functioning and physical ability[52, 53, 214, 220]. **[Au: merged paragraph]** Major long-term neurocognitive complications after CP include cognitive problems, particularly those affecting attention, working memory, episodic memory and executive function [53, 218, 219, 221, 222]. **[Au: please move the references such that they follow the cognitive problem in the list, enabling readers to easily go to the reference they need]** Reduced performance scores for executive functioning and memory in childhood-onset CP have also been reported[223]. Educational and psychological deficiencies were also observed in long-term CP survivors after primary subtotal surgical resection followed by radiotherapy[219]. Reported neurocognitive impairment include behavioural instability, attention problems, memory disturbances and slower cognitive speed[218, 219, 221]. In up to 82% of patients, intact intellectual functioning has been observed[218, 219].

Studies on interventional efforts to treat neurocognitive deficiencies are rare. Case studies suggest that functional behavioural analysis and goal management therapy are useful diagnostic and therapeutic options for cognitive rehabilitation, compensating for cognitive and psychosocial impairments[224].

[H1] Outlook

[Au: text in green moved up to serve as an introduction to this section ok?] Professional expertise in diagnostics and treatment has relevant impact on outcome and prognosis after CP[116, 145, 236-240]. **[Au: please consider citing fewer references here]** Accordingly, the Pituitary Society has published criteria for centres of excellence for treatment of pituitary tumours[241]; professional societies and health authorities should support this effort to assure diagnostic and therapeutic quality. However, such centralization includes high thresholds concerning infrastructure not achievable in all health care systems. Alternatives such as multicentre-based networks for reference assessments should be considered to assure high standards of treatment quality[242, 243]. Alongside infrastructural improvements, efforts are underway to develop better treatments for CP, for example, targeted therapies, and to improve prognosis overall. **[Au: leader sentence add for flow ok? Feel free to edit as appropriate]**

[H2]Targeted therapy [Au: subheading added to break up text ok?]

Novel insights in molecular pathogenesis of CP have opened up new perspectives on targeted therapy in these tumours. The molecular profiling of mouse and human ACP has revealed potential pathways of therapeutic relevance, which can be targeted using clinically approved small-molecule inhibitors[8, 90]. For example, vismodegib, a clinically approved SHH pathway inhibitor, has been successfully used to treat medulloblastoma and basal cell carcinoma, both tumours being driven by over-activation of the SHH pathway[225, 226]. However, inhibition of the SHH pathway has recently been shown to lead to increased cell proliferation and accelerated tumour formation in both mouse and human ACP, indicating this therapy should not be attempted in the patients and reinforcing the notion that preclinical research must be performed prior to repurposing drugs against other tumours[88]. Another avenue to explore is the inhibition of the MAPK pathway using trametinib, a specific MEK

inhibitor[227, 228], which reduces the proliferative index and increases apoptosis of tumour cells in explant cultures of both mouse and human ACP[8].

In cystic CPs, intracystic therapies have been used with variable results. In a recent review of 56 children with ACP, it was shown that intracystic interferon-alpha delays disease progression and is safer than other therapeutic modalities (Kilday et al., Neuro Oncol. 2017 Oct 1;19(10):1398-1407. doi: 10.1093/neuonc/nox056. Intracystic interferon-alpha in pediatric craniopharyngioma patients: an international multicenter assessment on behalf of SIOPE and ISPN. Kilday et al. Although the mechanisms underlying the effects of interferon alpha are elusive, these are likely to be related to the anti-inflammatory roles. The important inflammatory nature of ACPs suggests that novel therapies aiming to inhibit cytokine signalling may be of relevance. Indeed, using IL-6 or IL-1 inhibitors are already available for other indications. Supporting this, a recent study has shown promising results in treating cystic ACP by systemic administration of IL-6 inhibitors (Reference: Grob et al., Targeting IL-6 Is a Potential Treatment for Primary Cystic Craniopharyngioma Front. Oncol., 21 August 2019 | https://doi.org/10.3389/fonc.2019.00791. Additionally, the use of PD-1 inhibitors may be of relevance in ACP and require preclinical evaluation.

Regarding PCP treatment, the identification of *BRAF-V600E* mutations has prompted the use of combinatory therapies with BRAF and MEK inhibitors (for example, dabrafenib and trametinib) with good results[229-232]. An ongoing national phase II trial (ClinicalTrials.gov NCT03224767) is currently analysing safety, tolerability and pharmacokinetics of vemurafenib and cobimetinib medication in patients with *BRAF-V600*-mutation positive PCP.

[Au: can you mention issues of bioavailability to the brain for systemic therapy approaches? Would it be 'easier' to reach the cystic ACPs vs the solid PCPs? Strategies to overcome this? Yes see above]

Efforts in molecular research should also focus on the elucidation of pathogenetic mechanisms underlying hypothalamic involvement in CP. As hypothalamic syndrome and its sequelae are major causes for impaired QOL, targeted therapies aimed against tumour progression may not be suitable to substantially improve outcome in patients with primary hypothalamic involvement of their tumour

[233,161].

[H2] Surgery and radiotherapy[Au: subheading added to break up text ok?]

[Au: edited to avoid repetition] External radiotherapy is efficient in controlling and preventing progression and recurrences[234]. Due to its physical characteristics, proton beam therapy offers advantages over photon irradiation in terms of sparing surrounding tissue, thereby, decreasing the risk of sequelae. However, studies on long-term outcome after proton beam therapy are needed to prove this hypothesis. Considerable debate abounds whether irradiation of residual tumour after incomplete resection should be performed immediately after surgery or at the time of progression of residual tumour. Unfortunately, a prospective, randomized trial analysing this question could not definitively answer this question[235].

[H2]Adverse effects

During recent years our knowledge on neurpsychological adverse effects of CP has substantially increased. However, efficient therapeutic options to treat hypothalamic syndrome and its most predominant clinical manifestations (obesity and neuropsychological deficiencies) are currently not available. Accordingly, further studies aiming at efficient interventions for treatment and/or prevention of hypothalamic sequelae in these patients are necessary.

Furthermore, to improve prognosis and rehabilitation in CP patients at highest risk for reduced QOL, studies focused on molecular mechanisms of hypothalamic tumour invasion and trials analysing therapeutic options for patients with hypothalamic syndrome are warranted. Due to the rareness of the disease, common international efforts in research and treatment are recommended and should lead to an international registry for childhood-onset CP as a first step towards efficient coordination of scientific and clinical initiatives.

In conclusion, future efforts to improve prognosis, outcome and QOL in patients with CP should be focused on improving understanding of molecular pathogenesis of CP, with the perspective of

961 developing targeted therapies effective against progression and hypothalamic involvement; surgical
962 and radio-oncological treatment strategies, aiming at hypothalamus-sparing approaches to prevent
963 sequelae; treatments and interventions for hypothalamic obesity and neuropsychological sequelae after
964 CP; political efforts to establish and confirm criteria for quality of multidisciplinary treatment of CP;
965 and infrastructure in LMICs in particular to provide equitable care across the world **[Au: We don't**
966 **usually have lists in the main text, so rewritten to prose OK?]**.
967

Box 1. Factors when considering surgery in CP

Several key questions must be considered before undergoing gross total resection (GTR) surgery for craniopharyngioma (CP), especially in children **[Au:OK?]**. The first series of questions involves sequencing. Is a staged approach appropriate whereby the tumour is removed piecemeal **[Au:OK?]**? **[Au: what are the questions to consider when staged surgery is considered? This was suggested by the referees.]** Most agree that the first attempt at resection is often the best time to achieve complete resection[1, 57, 244]. For a patient presenting with severe symptoms related to hydrocephalus, can decompression of the ventricles or restoration of the flow of cerebrospinal fluid be achieved without compromising an attempt at GTR **[Au:OK?]**? For a patient presenting with visual compromise, should they be referred to an expert team to attempt GTR? Is near-total resection a reasonable approach to delay external beam radiotherapy? In the end, any tumour can be removed; however, the risks may be unacceptable. Which raises the question of what risks are acceptable. Do patients, including children and their parents, understand the risks of GTR? If the stalk can be preserved, GTR leads to diabetes insipidus in 50% of patients[26]; if the stalk is sacrificed, diabetes insipidus is an inevitable consequence. Do patients understand the implications of diabetes insipidus enough to accept it as a treatment-related complication? Given other potential treatment options, should diabetes insipidus and endocrinopathy be part of the decision-making process[26]? Amongst all treatment options, the appropriate use of GTR relies heavily on patient selection. Thus, how can selection for GTR be improved? Estimating the proportion of cases that might be eligible for surgery alone is currently difficult. Accordingly, the decision-making process is complex and needs to be optimized for each individual patient. **[Au: edits OK?]**

Box 2. Global variation in diagnosis and management of CP

Global variations and the burden of treating craniopharyngioma (CP) around the world is difficult to comprehensively assess as reports from low and middle-income countries (LMICs) are lacking. In some publications, childhood and adult-onset CP cohorts are mixed[245] or paediatric CP is discussed at the time of relapse[234]. Other reports are focused on the surgical approach[246] or on the clinical and morphological presentation without description of associated comorbidities[247]. A publication from Nigeria[248] reported a high postsurgical mortality rate (32%) that has not been observed in other series (7% in Turkey[249] and 6% in Jordan[250] and Egypt[246]). Amayiri *et al.*[250] reported on the Jordanian experience in treating paediatric-onset CP, observing a 5 year overall survival of 87±7%, which is similar to high-income countries. However, in their study, the quality of life of surviving children was impaired owing to comorbidities and difficulties in integration to school and, later, professional life. The authors attributed these difficulties to delayed presentation, to referral **[Au: to experts in CP?]** after initial surgical intervention by neurosurgeons with limited expertise in CP and to limited community rehabilitation resources. A multidisciplinary team approach is ideal for decision making, but LMICs are less likely to have experienced multidisciplinary team members, expert facilities and supportive services (social workers, psychologists and school integration services) to optimize outcomes. Accordingly, the multidisciplinary team needs to consider the availability of resources for treatment and future follow-up when considering their treatment decisions.

Box 3. Factors when considering radiotherapy in craniopharyngioma.

[Au: Edited for brevity; please check carefully]

The recommendation for radiotherapy, especially in children, should be made after careful consideration by the care team and should be discussed with the patient and their family in detail. **[Au: sentence moved up for flow]** Any treatment, procedure, complication or medication that results in increased intracranial pressure or reduced blood flow (surgery, shunt placement or revision, hydrocephalus, prolonged anaesthesia or sedation) or sensitizes the brain to the effects of radiation (certain medications, nutritional supplements or chemotherapy agents) may increase the risk and severity of adverse effects. Indeed, anticipated adverse effects depend on many factors, including the extent and prior effects of the tumour, the extent and prior effects of treatments including surgery, and patient factors including age.

The short-term adverse effects during radiotherapy generally increase during the treatment course, can be treated and subside at the completion of treatment; however, some may linger, especially fatigue. Short-term adverse effects may include nausea, vomiting, headache, fatigue and loss of appetite. Hair loss corresponding to the entrance and exit points of radiation beams may occur. If residual tumour is present, aspiration of cyst contents may be required. Surgery to reduce **[Au: improve?]** visual pathways or maintain cerebrospinal fluid (CSF) flow may be required. Optimization of the cystic and solid tumour complex prior to irradiation may obviate the need for intervention during radiotherapy.

Of greatest concern are the long-term adverse effects, especially those that can be severe or life-threatening, the incidence and severity of which often depend on the age of the patient at the time of treatment, the volume of irradiated brain, and complications arising from the tumour or prior treatment. Hormone deficiencies can develop, hearing loss is possible when any portion of the hearing apparatus (middle and inner ear or brainstem) is included in the treated volume, and vision loss can rarely occur despite radiation doses being lower than the tolerance of the optic nerves and chiasm. Radiotherapy may affect cognitive function — specifically memory, attention, learning, behaviour, academic ability, general intelligence and overall performance in work or school. Radiation decrease

the growth of bone or soft tissues included in the treated volume. Permanent hair loss may occur. Although the doses of radiation used are generally accepted as safe, necrosis can occur and lead to permanent neurological damage or death. Similarly, the risk of vasculopathy and stroke are low. With any type of radiotherapy, risk of secondary neoplasms cannot be avoided.

Figure 1. Features of craniopharyngioma.

Clinical and histopathological characteristics of adamantinomatous craniopharyngioma (ACP) and papillary craniopharyngioma (PCP). The dashed lines represent possible origin of these tumours.

Figure 2. Pro-tumourigenic effects of senescence and SASP in mouse and human ACP

A: In inducible mouse model of adamantinomatous craniopharyngioma (ACP), the expression of oncogenic β-catenin in embryonic precursor cells or young adult pituitary stem cells that express the transcription factor SOX2 results in the formation of cell clusters. These cell clusters become senescent and activate the pro-tumour senescence-associated secretory phenotype (SASP). The activities of the SASP signals (which include growth factors, cytokines, chemokines, proteases and extracellular matrix components) induce transformation of a surrounding cell, which becomes the tumour-initiating cell, in a paracrine manner. Thus, the cell sustaining the oncogenic 'hit' (the $SOX2^{+}$ cell) and the tumour-initiating cell are different. Senescent cells within the clusters and tumours continue secreting factors that fuel tumour growth. **B**: In human ACP, evidence supports a role of the SASP activities of the senescent cells, either sporadic single cells or clusters, in tumour growth by a variety of mechanisms, including epithelial tumour-cell proliferation and tumour invasion. Indeed, the location of clusters in the base of the finger-like protrusions at the invasive front of the tumour suggest a role of the SASP activities in tumour invasion. These activities might also contribute to cyst formation. BMPs, bone morphogenetic proteins; EGF, epidermal growth factor; FGF, fibrocyte growth factor; SHH, sonic hedgehog; TGFβ, transforming growth factor-β; TNF, tumour necrosis factor. **[Au: please confirm that this figure is original and has not been published previously. If not, please specify the origins of the figure in the Third Party Rights Table that I linked to in my cover email.]**

[Au: rearranged fig 3 panels so they are references in order ok?] Figure 3. Neuroradiological characteristics of craniopharyngioma and other sellar masses.

A | Sagittal T1-weighted MRI after contrast application shows multiple isointense cysts around a small solid portion with enhancement of the cyst walls in a suprasellar, third ventricular craniopharyngioma.

B | Coronal T2-weighted MRI shows a mainly cystic, suprasellar, third ventricular craniopharyngioma with different signals of the various cysts and a probable calcified solid portion in the lower part of the tumour. **C |** Axial CT without contrast in the bone window shows a small hyperdense foci of calcification within the solid portion of a craniopharngioma. **D |** Axial early postoperative CT without contrast[15] shows a tiny calcification medial to the left anterior clinoid process**[Au: can you point this out with an arrow so we can compare with the MRI in panel E?]**. Note the postoperative air bubbles in the midline at the level of this calcification **[Au: can you point this out with arrows?]**. **E |** T1-weighted early postoperative MRI after contrast[15] fails to show the calcification depicted in panel D. The arrow denotes the area in which the calcification was visible on CT. **F |** T1-weighted enhanced MRI some months after resection[15] show a small cystic recurrence at the point of the tiny postoperative calcification **[Au: can you point this out with an arrow so we can compare with panel D and E?]**. **G** | T1-weighted sagittal MRI after contrast application shows a mainly cystic purely suprasellar, third ventricular craniopharyngioma with a small solid portion in the dorsocaudal part of the tumour and colloid in the most superior cyst (*).**H |** Spinal MRI reveals a spinal metastasis at level T12/L1 (arrow) 7 years after initial diagnosis of adamantinomatous craniopharyngioma[6]. **I |** **[Au: please provide an image of the cerebellopontine angle location; the original image for this panel was of a recurrence and has now been removed as it does not correspond to the reference in the main text]** **J |** Sagittal T2-weighted MRI shows a large chiasmatic-hypothalamic low-grade glioma **[Au: can you point this out with an arrow?]** with hyperintense signal as a hallmark of the low cellular density of this tumour type. **K |** Sagittal T2-weighted MRI showing a secreting germ cell tumour in the suprasellar area with an irregular internal structure and small cysts. A solid extension **[Au: can you point this out with an arrow?]** is seen in the thickened pituitary stalk and the sella turcica. **L |** Sagittal T1-weighted MRI after contrast shows a purely intrasellar cystic lesion **[Au: can you point this out with an arrow?]** between the anterior and posterior pituitary lobe that may represent a Rathke's cleft cyst.

[Au: please confirm that this figure includes only original panels. If not, please specify the origins of the previously-published panels in the Third Party Rights Table that I linked to in my cover email.]

Figure 4. CP with hypothalamic involvement: preoperative grading on MRI.

According to the system developed by Puget *et al.*[144], three grades of hypothalamic involvement have been defined. On sagittal T2 views: **A** | Sagittal T2 **[Au: weighted?]** MRI of a preoperative grade 0 craniopharyngioma (CP), with no hypothalamic involvement. The third ventricle floor is normal, the CP lies entirely below the sellar diaphragm (arrows). **B** | Sagittal T2 **[Au: weighted?]** MRI of a preoperative grade 1 CP, with compression of the hypothalamus that can still identified (from the mammillary bodies to the level of the infundibulum). A bulk and/or **[Au:OK?]** calcified portion of the tumour may have developed in the infundibulum **[Au: can you mark this with an arrow?]**. The sellar diaphragm is opened in its posterior part with an extension of the cystic part (asterisk). **C** | Sagittal T2 **[Au: weighted?]** MRI of a preoperative grade 2 CP in which the hypothalamus is unidentifiable.

[Au: please confirm that this figure includes only original panels. If not, please specify the origins of the previously-published panels in the Third Party Rights Table that I linked to in my cover email.]

Figure 5. Craniopharyngioma hypothalamic damage: postoperative grading on MRI.

[Au: In this figure we use roman numerals for the grades, but for the preoperative grading system in the main text we use Arabic numerals; please confirm these are correct for each system] De Vile *et al.*[176] defined different grades of postoperative hypothalamic lesions based on postsurgical hypothalamic imaging and body mass index (BMI) outcome[255] during follow-up. Hypothalamic damage results in weight gain and the development of hypothalamic obesity. Medians and interquartile ranges (in parentheses **[Au:OK?]**) are shown for BMI in standard deviations (SDs). Dashed white lines indicate the extent of surgical resection **[Au:OK?]**.

Table 1. Pharmacological intervention for hypothalamic obesity

Intervention	Mechanism of action	Patients (*n*) [Au:OK?]	Outcomes	Reference
Dextroamphetamine	Central stimulant; stimulation of noradrenaline and dopamine secretion, and dopamine reuptake inhibition	Paediatric CP (5)	Increase in physical activity, reduction in continuous weight gain, stabilization of BMI and improved daytime sleepiness	[194]
Dextroamphetamine		Paediatric CP (9), paediatric astrocytoma (2) and paediatric glioma (1)	Reduction in continuous weight gain, stabilization of BMI (10 of 12 patients) and improved daytime sleepiness (11 of 12 patients)	[195]
Dextroamphetamine		CP (3 paediatric, 1 adult), paediatric astrocytoma (1), paediatric ganglioglioma (1) and paediatric meningitis (1)	Reduction in continuous weight gain and stabilization of BMI	[196]
Methylphenidate	Central stimulant; dopamine reuptake inhibition	Paediatric CP (1)	Beneficial for weight gain	[197]
Octreotide	Somatostatin analogue; reduced pancreatic β-cell activation	Paediatric CP (13), paediatric astrocytoma (4), paediatric germinoma (1) and paediatric ALL (2)	Reduced insulin secretion, moderate to no improvement in BMI and increased risk of gallstone formation	[200]
Diazoxide and metformin	Reduced insulin secretion, reduced hyperglycaemia and improved insulin sensitivity	Paediatric CP (9)	Reduced weight gain, weight loss, peripheral oedema, emesis and elevated hepatic enzymes	[198]
Exenatide and liraglutide	GLP-1 receptor agonists; improved insulin sensitivity, increased satiety and reduced speed of gastric emptying	Adult CP (1), adult hamartoma (1), adult astrocytoma (1) and adult germinoma (1)	Improved cardiovascular profile, improved metabolic profile and sustained weight reduction	[201]
Fenofibrate and metformin	PPARα agonist; improved insulin sensitivity	Paediatric CP (10)	Improved insulin resistance, improved lipid profiles and no improvement in BMI	[199]

ALL, acute lymphoblastic leukaemia; BMI, body mass index; CP, craniopharyngioma, GLP-1, glucagon-like peptide 1; PPARα, peroxisome proliferator activated receptor-α.

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[Au: please update the reference list to reflect the editing changes]

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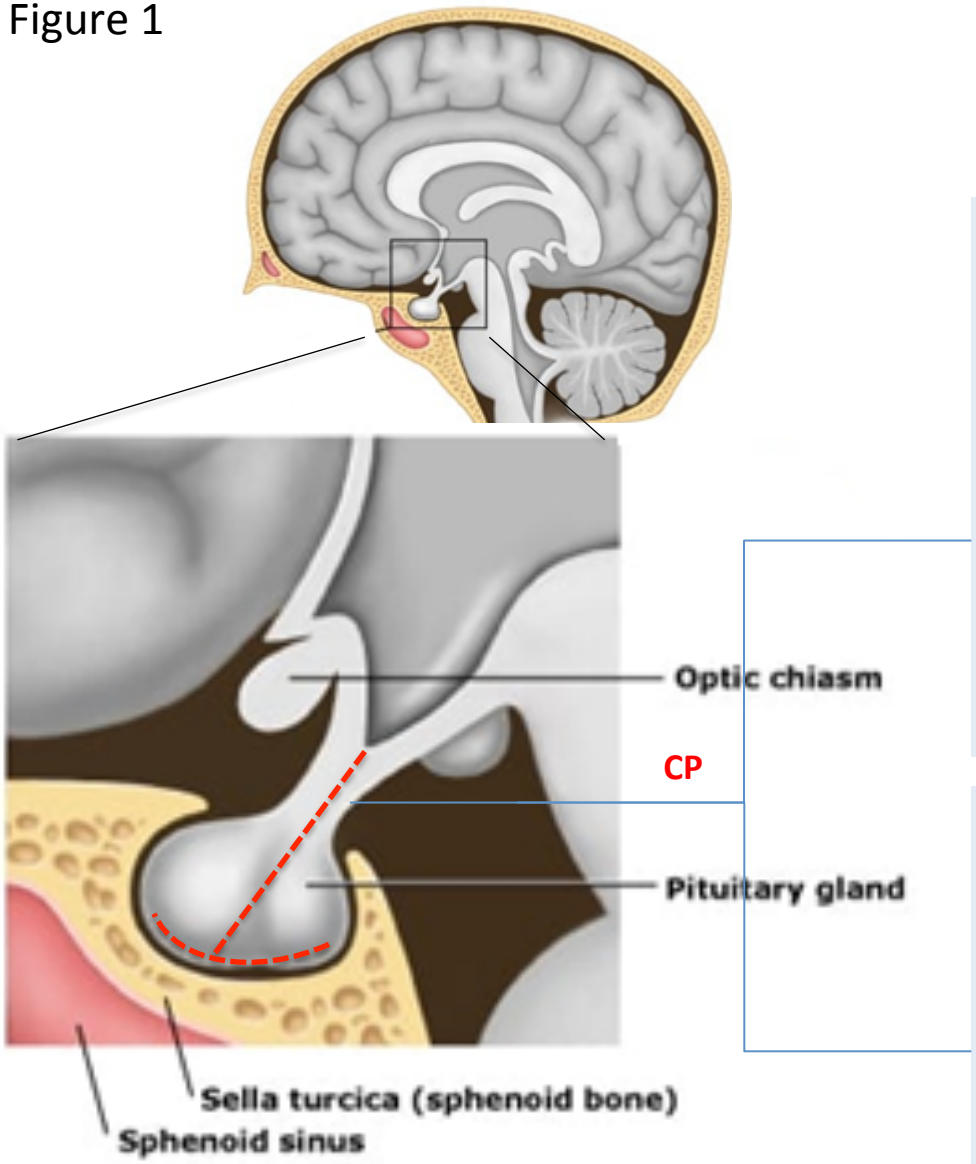
Figure 1



ACPs

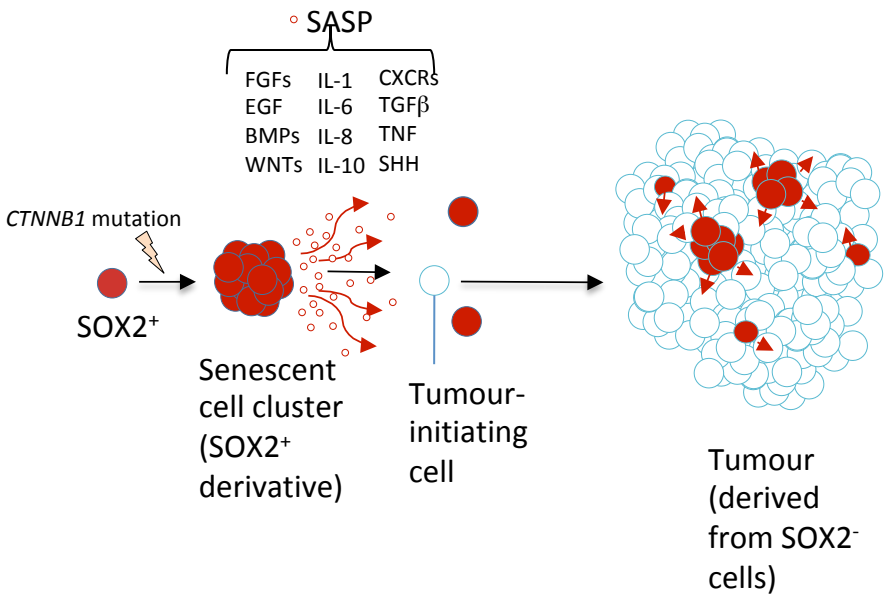
- Age of presentation: bimodal peaks at 5-15 and 45-60 years of age
- Cell of origin: embryonic remnants of the Rathke's pouch epithelium
- Appearance on MRI: 90% cysts, 90% calcifications, 90% enhancement
- Pathological features: distinctive epithelium that forms stellate reticulum, wet keratin, and basal palisades
- Key symptomology: visual impairment, headache, endocrine deficiencies

PCPs

- Age of presentation: 40-55 years
- Cell of origin: embryonic remnants of the Rathke's pouch epithelium
- Appearance on MRI: mostly solid rarely cystic tumours, without cholesterol-rich machinery oil-like fluid or calcifications
- Pathological features: fibrovascular cores lined by non-keratizing squamous epithelium
- Key symptomology: visual impairment, headache, endocrine deficiencies

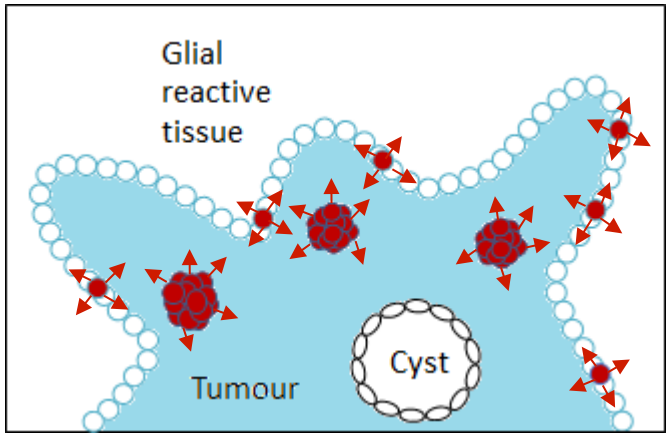
Figure 2

A. Mouse ACPs



→ Paracrine signalling from the senescent cells/clusters

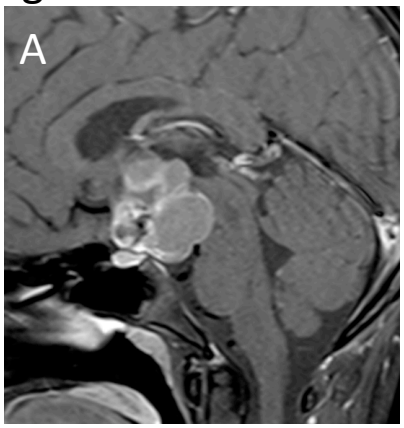
B. Human ACPs

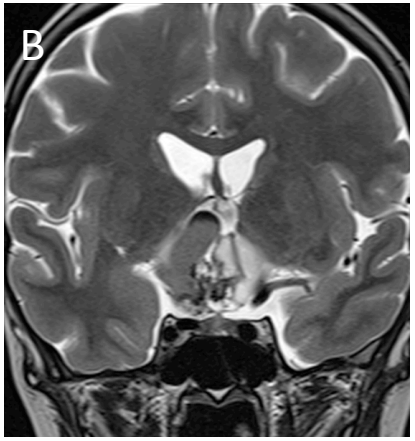


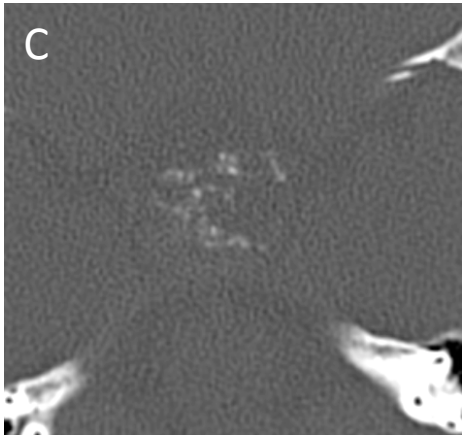
SASP pro-tumourigenic activities

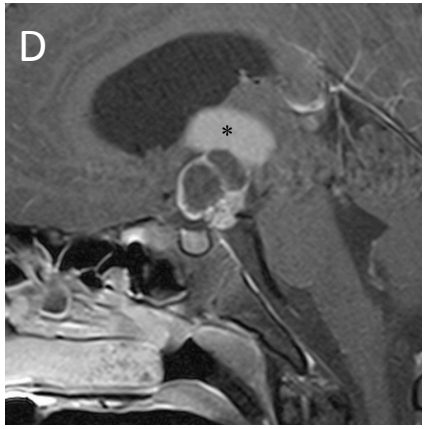
- Epithelial-mesenchymal transition
- Epithelial tumour-cell proliferation
- Tumour invasion
- Inflammation and cyst formation
- Suppression of immune surveillance

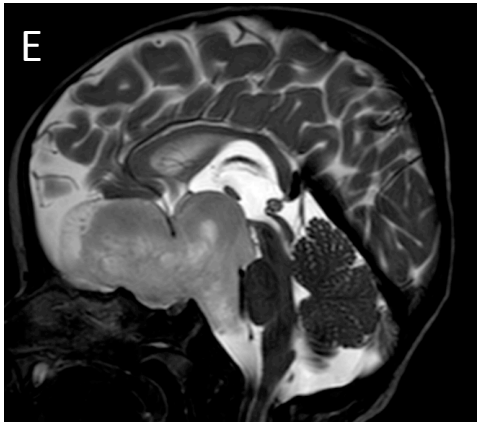
Figure 3

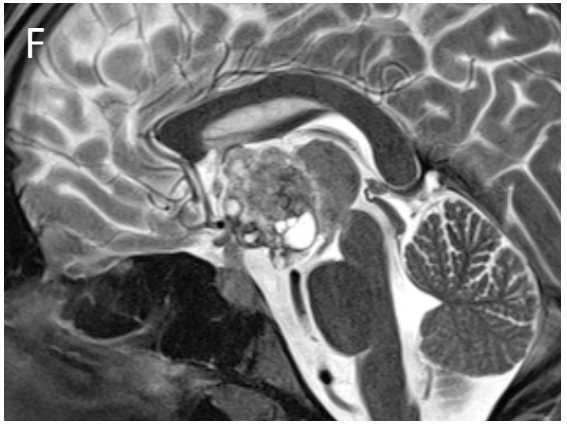


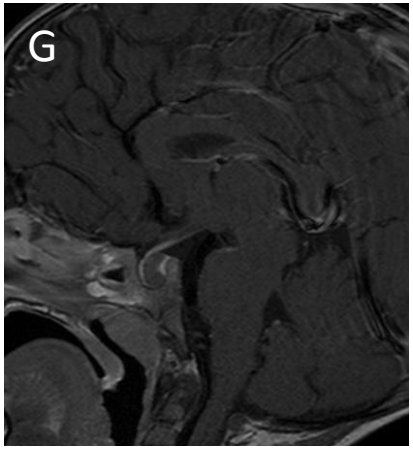


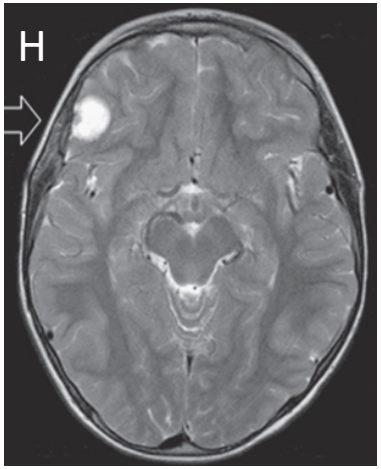












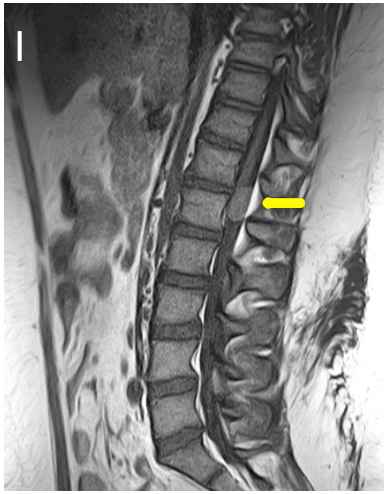


Figure 4

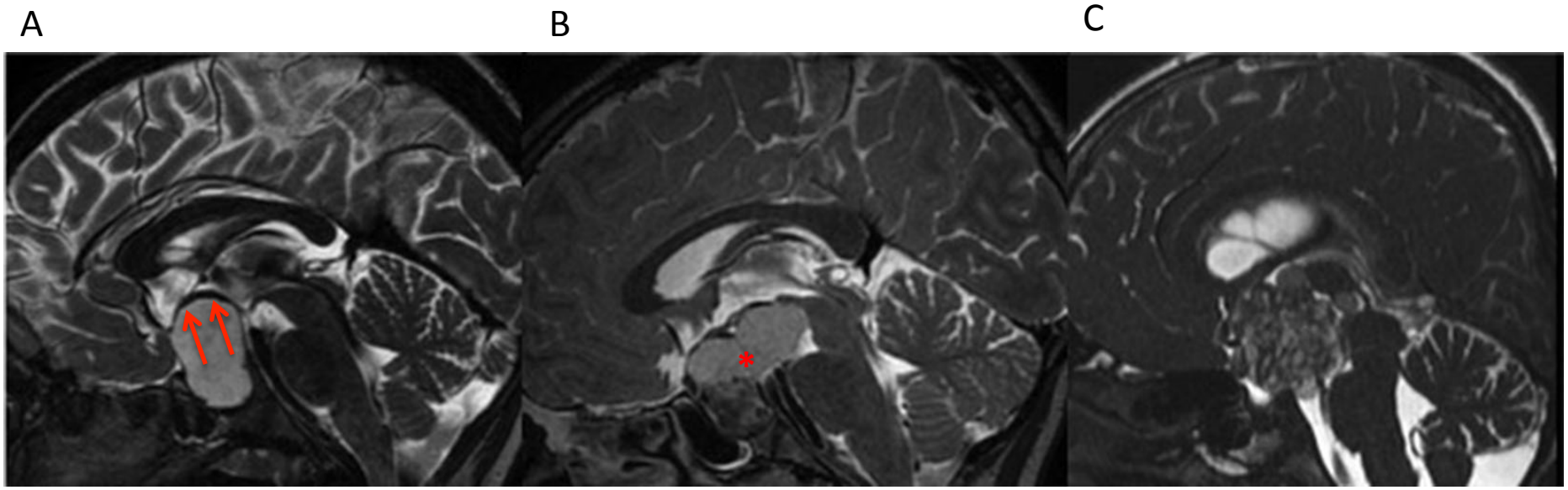
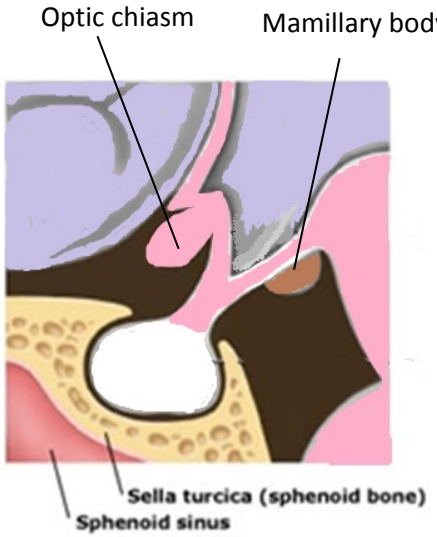
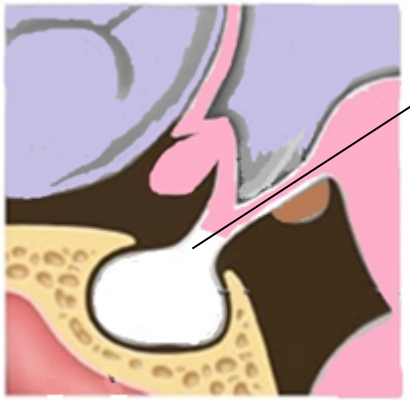
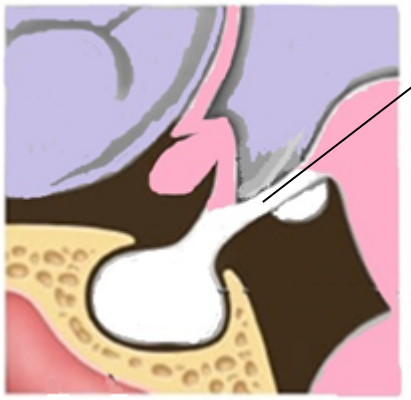


Figure 5

		Definition	Outcome
Grade 0		No discernable damage to hypothalamic structures	Stabilization of weight development BMI: 1.10 SD (0.1-1.3 SD)
Grade I		Abnormality of the of the floor of the 3rd ventricle and/or a breach in the tuber cinereum	Weight gain BMI: 2.5 SD (1.4-3.5 SD)
Grade II		Floor of 3rd ventricle completely deficient or extensively breached by residual tumour	Severe obesity BMI: 5.5 SD (4.3-8.8 SD)