Contemporary Biological Insights and Clinical Management of Craniopharyngioma

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Abstract

Craniopharyngiomas are clinically aggressive tumours due to their invasive behaviour and recalcitrant tendency to recur after therapy. There are two types based on their distinct histology and molecular features: The papillary craniopharyngioma (PCP), which is associated with *BRAF-V600E* mutations and the adamantinomatous craniopharyngioma (ACP), characterised by mutations in *CTNNB1* (encoding β-catenin). Patients with craniopharyngioma show symptoms linked to the location of the tumour close to the optic pathways, hypothalamus and pituitary gland, such as increased intracranial pressure, endocrine deficiencies and visual defects. Treatment is not specific and mostly non-curative, and frequently includes surgery, which may achieve gross-total or partial resection, followed by radiotherapy. In cystic tumours, frequent drainage is often required and intracystic instillation of drugs has been used to help manage cyst refilling. More recently targeted therapies have been used, particularly in papillary craniopharyngioma, but also now in adamantinomatous craniopharyngioma and clinical trials are underway or in development. Although patient survival is high, the consequences of the tumour and its treatment can lead to severe comorbidities resulting in poor quality of life, in particular for those patients that bear tumours with hypothalamic involvement. Accordingly, in these patients at risk for the development of a hypothalamic syndrome hypothalamus-sparing treatment strategies such as limited resection followed by irradiation are recommended. In this review, we provide an update on various aspects of craniopharyngioma, with emphasis on recent advances in the understanding of tumour pathogenesis, clinical consequences, management and therapies.

Introduction

While craniopharyngioma is a WHO grade I tumour, it is anything but benign [1]. Given the tumour's close proximity to the optic chiasm and nerves, the circle of Willis, the pituitary and hypothalamus, its potential to adversely affect vision, endocrine function, hypothalamic function, cerebrospinal flow, and vascular injury is great. Patients with craniopharyngioma are at high risk of developing tumour and treatment related morbidities that adversely impact a patient's quality of life [2]. Because these tumours are difficult to remove without causing injury to one of the surrounding critical structures, radiotherapy often plays a very important role in patients with either a subtotal resection or a conservative surgical procedure intended to either confirm the diagnosis or restore function through decompression of the optic nerves and chiasm or re-establishing cerebrospinal flow. Care for craniopharyngioma patients requires a multidisciplinary approach to optimally manage the endocrine, neurosurgical, and other medical issues that arise because of the tumour and its treatment [3,4]. Therefore, the histologically benign nature of these tumours according to the WHO classification is misleading, as up to 50% of these tumours can behave clinically aggressively.

Craniopharyngiomas are diagnosed at any stage of life, however, the adamantinomatous type (ACP) is the most common non-neuroepithelial intracranial tumour in children (<18 years of age) and has a bimodal distribution (5–15 years and 45–60 years) [5]. ACP accounts for around 5–11% of intracranial tumours in the paediatric age group [6]. In contrast, PCP is predominantly an adult tumour, occurring only rarely in children [5].

Research in murine models and human tumours has revealed important insights into the aetiology and pathogenesis of these tumours. Likewise, advances in neuroradiological imaging, surgical approaches and radiotherapy have resulted in better tumour control and reduced complications. Nonetheless, quality of life remains low for many survivors and there is a need to identify novel risk-appropriate treatment options for this frequently chronic disease.

In this review, we provide an update on craniopharyngioma and in particular we expand on four areas: (i) the genetics and pathogenesis of craniopharyngioma, where we integrate data from

murine and human tumours and discuss the potential role of cellular senescence and inflammation in tumour growth and invasion; (ii) (neuro)endocrine and neuropsychological sequelae and treatment options with special regard to hypothalamic syndrome, due to tumour and/or treatment-related hypothalamic damage; (iii) discussion of surgical approaches to craniopharyngioma, including the importance of multidisciplinary decision making, goals of surgery and the most commonly employed operative corridors; (iv) the role of radiotherapy in treatment, its efficacy and treatment related side effects.

Genetics of Craniopharyngioma

The histological features of the two types of craniopharyngioma, adamantinomatous and papillary are well described (**Figure 1**) [7]. The genetic distinctions have also been well delineated, with ACP characterised by activating *CTNNB1* (gene encoding β-catenin) mutations and PCP with activating *BRAF-V600E* mutations [8]. The *direct* consequences of such mutations are the activation of two different signalling pathways: The WNT/β-catenin pathway in ACP and the mitogen-activated protein kinase (MAPK) pathway in PCP [8]. Of note, other downstream pathways are activated *indirectly*, e.g. the MAPK pathway is also activated in ACP tumours around the invasive front (Invasive front: the interface between the palisading epithelium and neighbouring reactive glial tissue). [9].

In recent years, several studies have reaffirmed this distinction, through sequencing of these genes with a variety of methods [10-13]. He and co-workers have published the first whole genome sequencing characterisation of CP, showing mutual exclusivity of *CTNNB1* mutations, in 11 of 16 ACPs, and *BRAF-V600E*, in 7 of 10, PCP[10]. The authors have also characterised a novel transversion and in-frame deletion of *CTNNB1* that can activate the WNT/β-catenin pathway [10]. This study has confirmed the low mutational burden, previously observed in craniopharyngioma [14], and the absence of recurrent functionally significant mutations in their cohort. Using an ultrasensitive next generation sequencing technique, called targeted amplicon sequencing, *CTNNB1* mutations have

been identified in 100% of 19 ACP, suggesting that the lack of identification of mutations previously described in some tumours, may reflect sampling with low epithelial tumour content and lack of sensitivity of approaches such as Sanger sequencing used in other studies [11]. However, biallelic inactivating mutations of *APC* (adenomatous polyposis coli, a negative regulator of the WNT/β-catenin) in the absence of *CTNNB1* mutations have been described in two ACP tumours, suggesting other alterations are possible [15]. However, if there are other genomic alterations in ACP resulting in the activation of the WNT/β -catenin pathway, these are exceptionally rare. As genome sequencing becomes part of standard practice for brain tumour patients in many centres, it is likely that over the next decade, the genomic landscape of craniopharyngioma will become increasingly well defined. Reflecting these differences in histology, genetics, but also demographic, radiology and methylation profiles, ACP and PCP are now considered distinct tumour types within the WHO 2021 classification, as opposed to subtypes, as they were in previous editions [1].

Mouse Studies in Craniopharyngioma

Expression of BRAF-V600E in murine SOX2 pituitary progenitors does not form tumours, but instead results in the induction of cellular senescence and apoptosis, suggesting that other hits may be required to initiate the oncogenic process [16,17]. Nonetheless, these mouse studies have shown that expression of BRAF-V600E in early anterior pituitary precursors result in increased proliferation and expansion of the SOX2 stem cell compartment as well as a blockade in terminal differentiation of committed lineage precursors. These studies led to the realisation that despite the presence of *BRAF-V600E* mutations in all tumour cells in human PCP, the activation of the MAPK pathway (i.e. expression of phospho-ERK1/2, a read out of active signalling) occurs in a minority of tumour cells, mostly lining the fibro-vascular cores (**Figure 1**), which co-express SOX2 [16]. Moreover, the vast majority of the proliferative cells in human PCP are contained within the SOX2+ cells lining the fibro-

vascular cores [16]. Therefore, although these mouse models do not form tumours they have helped understand better the pathogenesis of human PCP.

Mouse research has been very informative in ACP. Murine models have demonstrated that *CTNNB1* mutations are oncogenic drivers, since expression of a functionally equivalent form of mutant β-catenin to that described in human ACP in murine SOX2+ embryonic progenitors or adult stem cells result in formation of tumours that are reminiscent of human ACP [18,19]. Analyses of these murine models coupled with molecular profiling of human ACP, have suggested a central role for a minority of tumour cells, mostly grouped in epithelial whorls (also referred as cell clusters) but also dispersed throughout the tumour epithelium, in ACP pathogenesis [18-21]. Activation of the WNT pathway, as evidenced by nuclear localisation of β-catenin and expression of downstream targets e.g. *AXIN2* and *LEF1* is restricted to these subsets of tumour cells (**Figure 1**) [18-21]. The nuclear β-catenin accumulating clusters have been shown to express stem cell markers (e.g. CD44, CD133) and to be senescent with activation of a senescence-associated secretory phenotype (SASP) [20,22]. The SASP includes a plethora of secreted factors including growth factors, inflammatory mediators (e.g. cytokines, chemokines) as well as extracellular matrix modifiers, which have been confirmed to be expressed by these clusters in mouse and human tumours [9,20,21]. Manipulation of the SASP in mouse models suggests a critical role of these factors in tumour growth, where reduction in expression inhibits the development of tumours [20]. These clusters also show similarity to the enamel knot, a critical paracrine signalling structure in the developing tooth, consistent with other molecular and histological similarities between ACP and tooth development [9]. Laser capture microdissection and mutation specific antibodies have confirmed the presence of the *CTNNB1* mutation throughout the tumour epithelia and not just in cell clusters, but the reasons underlying β-catenin nuclear localisation in such restricted manner are not yet understood [11]. Therefore, murine studies, mostly for ACP, have revealed important insights into the pathogenesis of these tumours.

Secondary Downstream Pathways in Craniopharyngioma

The initial activation of the MAPK pathway in PCP or the WNT/β-catenin pathway in ACP results in the activation of other downstream signalling pathways. Little is known about these pathways in PCP, however, considerable knowledge has been accumulated in the last 5 years regarding these downstream effects in ACP.

High levels of sonic hedgehog (SHH) expression have been identified in ACP through transcriptional profiling of human tumours and murine models [9,21,23,24]. Not only the mRNA but also SHH protein has been shown to be expressed in the senescent cluster cells [25]. Cells within the clusters and palisading epithelium show upregulation of downstream targets such as GLI1 and GLI3, suggestive of both autocrine and paracrine signalling [24]. Whilst higher expression of pathway inhibitor genes *SMO* and SUFU appeared to correlate with longer progression free survival there was no correlation with other markers of pathway activation such as GLI1 [24]. Functional evaluation in the genetically engineered mouse model and in human ACP tissue *ex vivo* has shown that SHH pathway inhibition, by the drug vismodegib, promoted tumour proliferation and growth, and reduced the lifespan of mice, through increasing the proportion of clonogenic cells [25]. Consequently, targeting SHH is no longer considered an appropriate therapeutic opportunity for ACP.

Members of the TGF family of secreted factors have been identified to be expressed in the senescent clusters, (e.g. TGFβ, BMP4, BMP7) [9,21]. Moreover, activation of phospho-SMAD1,5,8,9 and phospho-SMAD3 demonstrate activation of the pathways in cells in proximity to the clusters [9]. These factors play important roles in tooth differentiation. With an overlap in processes between odontogenesis and osteogenesis, it has been shown that BMP2 can induce osteoblastic differentiation and cell calcification in ACP cells [26].

Several factors able to activate the MAPK pathway are expressed in the cluster cells, e.g. FGFs (e.g. FGF3, 4, 9, 19, 20), EGF, PDGF [9,21]. This finding has led to the demonstration that the MAPK/ERK pathway is also activated in both human and mouse ACP [9]. Immunostaining against pERK1/2 (a read

out of activated MAPK pathway) has shown MAPK pathway activation mostly in the invasive front, i.e. the interface between the palisading epithelium and neighbouring reactive glial tissue, with possible spatial co-localisation with proliferative (Ki67+ve) cells [9]. Subsequently, other studies have confirmed activation of the MAPK pathway in ACP, including a large phospho-proteomics study, in which ACP tumours have been shown to group with low-grade gliomas, the latter being tumours driven by activation of the MAPK pathway due to genomic alterations in components of this pathway [27,28]. Inhibition of the MAPK pathway in human and murine ACP tumour tissue *ex vivo* reduce proliferation and increase apoptosis, suggesting that targeting this pathway may be of therapeutic value for ACP patients [9]. More recently further functional studies have suggested that the immune inhibitory cell membrane protein CD47 promotes proliferation and migration of adamantinomatous craniopharyngioma cells by activating the MAPK/ERK pathway [28]. One case report of a patient bearing an aggressive ACP tumour responding to binimetinib has been published, showing an approximately 50% reduction in tumour volume with therapy [29]. Currently clinical trials are under development for the evaluation of MAPK inhibitors in ACP.

Other developmental pathways are activated in ACP, particularly in the clusters, such as the Hippo and Ectodysplasin pathways, however so far little is known on their functional relevance [9,30]. Advances in cell culture (e.g. organoids) and *ex vivo* explants in combination with mouse models will enable the functional evaluation of these and other pathways [9,28,31,32].

Inflammation in ACP

In addition to growth factors, inflammatory mediators are also secreted by senescent cells in ACP including IL1A and IL6 [33]. These and other inflammatory mediators, e.g. IL8, IL1B, MCP1 and CXCL12 have been identified within ACP tissues and cyst fluid by several groups and the pattern of cytokines is suggestive of activation of the inflammasome, an innate immune effector mechanism that results in a pro-inflammatory cascade [9,33-36]. These results are further supported by the expression of

P2X7R, an inflammasome component within the senescent clusters, and the reduced expression of IL6, IL8 and MCP1 upon knock-down of P2X7R *in vitro* [37]. Cell culture experiments have been used to try to understand the role of these cytokines on tumour cells, which show that IL6 promotes an epithelial to mesenchymal transition (EMT) and increases migration of ACP cells [33]. Reduced E-cadherin and increased vimentin expression, markers of EMT, have previously been found to be associated with ACP recurrence, together suggesting IL6 may promote tumour growth [38]. In patients with cystic ACP, treatment with the IL6 inhibitor tocilizumab has been shown to cause a significant response [39]. Surrounding the tumour epithelia in ACP there is often a profound glial reaction that includes microglia and other immune cells (e.g. macrophages). Immune cell receptors, such as the IL6R are expressed both within tumour epithelia and reactive tissue, suggesting cell-cell communication [33,36]. Immuno-histochemical studies have shown a range of cell types present in the glial reactive tissue including macrophages, microglia and T lymphocytes [9,40,41].

Some studies have attempted to correlate the immune environment with clinical characteristics. In one study high levels of CXCL12 and CXCR4 expression were associated with ACP recurrence [42]. Another study has shown higher levels of cytokine expression to be associated with greater histological inflammation and worse endocrine function in patients with infra-diaphragmatic ACP, which is consistent with *in vitro* and *in vivo* evidence suggesting that inflammatory cytokines, such as IL1A can affect hormone secretion [43,44]. The use of systemic markers of inflammation to support the diagnosis of ACP has been suggested, however this remains to be validated in independent cohorts [45].

Expression of anti-inflammatory mediators, e.g. IL10, and immune checkpoint proteins, particularly PDL1, has also been observed in human ACP, though with some variation in patterns and rates of positivity described across papers [9,28,36,41,46-48]. The high expression of PDL1 within ACP has suggested that PD1 inhibitors could be used as therapies for craniopharyngioma. Currently there is only one case report in the literature of a patient, with recurrent ACP, who was treated with the PD1 inhibitor nivolumab and was reported as having stable disease but subsequently discontinuing treatment due

to progression [49]. Expression of the inhibitor protein B3-H7 has also been described with expression correlating negatively with T cell infiltration. In vitro experiments using a

B7-H3/CD3 bi-specific T cell engager (BiTE) showed inhibition of growth of human primary cranio-pharyngioma cells in a time- and dose-dependent manner, suggesting a potential therapeutic opportunity from modulation of this pathway [50]. CD47, an immune inhibitory membrane protein is also highly expressed on the palisading epithelium. Inhibition of CD47 in *in vitro* experiments increased phagocytosis of ACP cells [28]. As highlighted above, as CD47 also activates the MAPK pathway in ACP and therefore targeting of CD47 in ACP is of therapeutic interest [28].

Laser capture microdissection and *in silico* approaches such as cibersort have been useful in the identification of many inflammatory mediators, it is likely that single cell sequencing experiments will be more informative and reveal cell-cell interactions [9,51]. *In vivo* functional experiments will be required to understand the contributions of different cell types and pathways in tumour pathogenesis as well as hypothalamic and endocrine deterioration in the patients. As an example of the latter, it has been shown that the orthotopic injection of cystic fluid into rats brains has a significant toxic and pro-inflammatory effect [52,53]. Likewise, using an elegant experimental approach in mice, it has recently been shown that injection of ACP cyst fluid in the hypothalamus results in the alterations in the expression of several regulators of growth and metabolism in hypothalamic neurons and mouse obesity. Additionally, neurodegenerative changes are observed with deposition of β-amyloid in the murine hypothalamus, a finding that is also conserved in human ACP [54] .

Anatomical and Morphological Considerations

In recent years, there have been many studies to better characterise the interface between the tumour tissue and normal structures, as well as to understand how different tumour presentations may help in deciding the optimum surgical management. Malluci *et al*. (2012) have highlighted in the Liverpool experience that some tumours initially involving the hypothalamus in the radiology images

may come away from the hypothalamus when cysts are drained, whilst others remained adherent [55]. Prieto *et al.* (2016) have performed a detailed topographical analysis of 500 cases described in the literature from autopsy and surgical studies between 1857 and 2016 to characterise five topographical variant of ACP and four grades of adherence to predict the risk of hypothalamic damage [56]. Pan *et al.* (2016) have analysed 226 tumours from a single centre experience in China to describe three patterns of growth, which they have subsequently further evaluated prospectively in a further 26 cases[57,58]. They describe: (i) Type Q tumours, which are most likely to involve the pituitary gland, do not invade the area of contact with the adenohypophysis but invasion is observed where the tumour contact the neurohypophysis; (ii) Type S tumours, which primarily involve the pituitary stalk with the arachnoid remaining present between the tumour and normal structures; and (iii) the most challenging Type T tumours, which are located beneath the basal arachnoid membrane with the pia mater disrupted and 'finger-like' invasions found in the neural layer of the third ventricle floor [57,58].

Radiological characterisation of the boundary and invasion of the hypothalamus has also been explored in numerous publications. The Paris criteria define three different patterns, Types 0-2 pre- and post- operatively, to grade hypothalamic injury, however, in the absence of well-defined radiological landmarks inter-observer consistency is difficult, which limits the use of this criteria in clinical practice [59]. Several groups have used the mammillary bodies as a landmark against which to assess hypothalamic damage [5,60]. For instance, CP studies in Germany have proposed a grading method, in which Grade 0 is a tumour without contact to the floor of the third ventricle, Grade I is a tumour with contact or compression of the hypothalamus anterior to the mammillary bodies, and grade II is a tumour that causes displacement, compression, or destruction of the hypothalamus at the level or dorsal to the mammillary bodies [61]. Pascual *et al.* (2013) have suggested using the mammillary bodies angle along other variables, including the position of the hypothalamus, presence of hydrocephalus, symptoms and patient age to define the topology [60]. A recent study has suggested the "eagle sign" combining the floor of the third ventricle, mammillary bodies and

cerebral peduncle to characterise four variants [62]. Machine learning approaches to radiological data have also been used to distinguish cases with finger-like invasions with those without on pathological evaluation [63]. Challenging the integration of these approaches into practice is the variation in imaging hardware, protocols and experience in interpreting the images. Multicentre cross-validation of these classifications and follow up are required to assess the long-term functional impact of changes to practice.

The biological mechanisms underlying tumour invasion have also begun to be explored. A tumour specific cellular environment has been identified by immunohistochemistry at the tumour/glial reaction interface showing distinct patterns of expression of nestin, MAP2 and GFAP along the invasive edge [64]. Apps *et al.* (2016) have mapped this interface in 3D using high-resolution micro CT imaging to show the presence of finger-like invasions and "balls on a chain" of connected islands of tumour. This study has highlighted a complex morphological relationship, in which senescent cluster cells with an activated SASP are present within the finger-like protrusions [65]. It has been shown that the MAPK pathway is activated in the invasive front, as evidenced by phospho-ERK1/2 staining in both palisading epithelium and glial reactive tissue close to the invasive tumour edge [9]. Of note, the location of the senescent clusters close to the invasive boundary suggests that paracrine signalling from these senescent cells through the SASP may regulate invasion in human ACP [9]. A graphical summary of these findings is depicted in **Figure 2**.

Clinical, neuroendocrine and quality of life aspects in craniopharyngioma

Pituitary deficits and neuroendocrine disturbances due to hypothalamic involvement and treatment-associated hypothalamic lesions [66] as well as visual [67,68] and neuropsychological impairments [69] have major impact on long-term prognosis and quality of life (QoL) after craniopharyngioma [5,67]. Furthermore, gender-specific [70,71], cardiovascular [72] and cerebrovascular sequelae such as cerebral infarction especially in patients with initial symptoms of increased intracranial pressure [73] result in

prognostic impairments. Recent publications on craniopharyngioma are focussing on risk-appropriate treatment strategies aiming at prevention or amelioration of the consequences of hypothalamic lesions as the cause of the most severe sequelae [5,61,74-78]. Areas of specific deficits after craniopharyngioma and the necessity of risk-appropriate rehabilitation efforts and interventions are: visual dysfunction, hyperphagia, sleep disturbances, decreased energy expenditure, hyperinsulinemia, hypopituitarism, psychosocial disorders, and QoL [79-81].

Visual dysfunction

Disturbances in visual acuity and visual fields are seen in approximately half of children at the time of initial diagnosis [67]. Visual impairment in children can have lifelong effects on self-perception, schooling, employment, as well as impacting daily functioning, and it has been shown that overall QoL correlates with visual acuity [68].

Hyperphagia

The fact that not all craniopharyngioma patients at risk develop hyperphagia may reflect the fact that hypothalamic involvement is variable and that despite hypothalamic involvement specific nuclei that modulate appetite may still be intact [82]. Management of hyperphagia starts with dietary and psychosocial counselling. Several pharmacological interventions have been analysed with regard to hyperphagia. Central stimulating agents such as dextroamphetamines may affect hyperphagia by inhibiting reuptake of norepinephrine, dopamine, and/or serotonin [83] [1]. Methylphenidate has been

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postulated to evoke a food reward response, to suppress pathological eating behaviour, and to exert beneficial effects on weight development [84]. Furthermore, studies of GLP-1 agonist effects on obesity and eating behaviour showed an improvement of hyperphagia symptoms and weight loss in most adult patients with hypothalamic obesity. Oxytocin-based pharmacological interventions for treatment of hyperphagia and obesity in hypothalamic syndrome are currently under investigation (NCT 02849743).

Bariatric interventions such as Roux-en-Y gastric bypass surgery may be considered as a last resort [90]. This very invasive intervention was shown to be effective in small studies in up to two years of follow-up, but recurrent obesity is observed and safety issues on endocrine substitution have been raised [91]. Furthermore, irreversible bariatric interventions such as gastric bypass surgery are sometimes not recommended in children due to ethical and legal considerations.

Sleep disturbances

Disturbances of sleep patterns may impact daily life, reduce energy expenditure, increase day-time sleepiness, and promote pathological eating behaviour such as desire to eat and BMI [92-95]. Early referral to specialized sleep clinics is the basis for decision on appropriate treatment of sleep problems [92]. Interventions may vary depending on the aetiology from coaching for worrying thoughts, anxiety or depression, improving sleep hygiene, to continuous positive airway pressure (CPAP) ventilation for obstructive sleep apnea syndrome.

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Decreased energy expenditure

Treatment of decreased energy expenditure is aiming at increasing the level of physical activity in combination with therapy of underlying causes for decreased energy expenditure such as pituitary deficits and disturbed sleeping patterns. Pharmacological treatment with central stimulating agents such as dextroamphetamines has been reported to increase resting energy expenditure (REE), and to improve feeding behaviour and energy expenditure [96] and stabilization of weight development [83]. Based on findings in animal models, oxytocin – a peptide hormone of hypothalamic origin - plays an important role in regulation of body composition by increasing energy expenditure and promoting weight loss [97,98]. In a case report, successful treatment of hypothalamic obesity with oxytocin and naltrexone has been reported in paediatric craniopharyngioma patients [88]. Zhang *et al.* [99] reported on the results of a pilot study of 8 weeks intranasal oxytocin administration in a small adult cohort group of adults leading to clinically relevant weight reduction of on average 8.9 kg associated with a reduction of waist circumference (appr. 10 cm), indicating a reduction in metabolically unfavourable visceral fat. In order to confirm safety and efficacy of oxytocin treatment for weight reduction after craniopharyngioma, larger clinical trials are warranted.

Hyperinsulinemia

Hyperinsulinemia management in craniopharyngioma patients is combining lifestyle modifications including physical activity and dietary modifications with pharmacological interventions [100-104]. Insulin concentrations in craniopharyngioma patients can be decreased by treatment with diazoxide and octreotide both inhibiting insulin secretion. A combination of metformin and diazoxide has been reported to promote weight loss and impaired glucose tolerance [85].

Pharmacological treatment with glucagon-like peptide receptor 1 (GLP-1R) agonists should be considered due to known effects of these satiety and gut-hormones, especially with regard to the

still intact gut-hypothalamic feedback loop after craniopharyngioma. GLP-1 medication results in decreased food intake presumably by binding to hypothalamic receptors in arcuate and dorsomedial nuclei, the vagus nerve and the hindbrain, as well the mesolimbic and hippocampus reward pathways. A 36-week regimen (once-weekly) with the GLP-1 agonist exenatide resulted in stabilization or reduction of obesity [105]. However, also less impressive effects with GLP-1 agonist therapy have been observed [86] especially in subjects with less hypothalamic damage as determined by MRI [106]. Besides increasing insulin sensitivity, metformin is known to reduce food intake by decreasing NPY- and AgRP-expressing hypothalamic neurons. However, no beneficial effects of metformin on BMI have been reported in craniopharyngioma patients, although decreased HOMA-IR (Homeostatic Model Assessment of Insulin Resistance) was observed. Oxytocin may also have positive effects on glucose homeostasis independent of effects on weight development due to increased insulin sensitivity and insulin secretion [107].

Hypopituitarism

Approximately 80–90% of patients develop complete pituitary insufficiency after surgical interventions for CP [108]. Patients surgically treated via transcranial approach more frequently present with pituitary deficits than patients treated transphenoidally [109]. In general, gross-total resection is associated with higher rates of post-treatment endocrinopathy than subtotal resection or subtotal resection plus irradiation; for certain endocrinopathies, the addition of irradiation increases the rate of deficient pituitary axes over subtotal resection alone [110].

Insufficient endocrine substitution is associated with a high risk of severe sequelae such as short stature or adrenal crisis [111]. GH replacement therapy (GHRT) that is initiated during childhood results in growth improvement without impacting overall- or progression-free survival [104]. GHRT in the presence of GH deficiency (GHD) does not increase the risk of craniopharyngioma relapse or progression [112-115]. Fixed intervals between the end of tumour treatment and the initiation of GHRT - as suggested in malignant cancers – are not necessary in craniopharyngioma patients with

GHD. GHRT beginning early after craniopharyngioma diagnosis may be associated with improvements in QOL and weight control [103]. Adult-onset craniopharyngioma patients present with 3- to 19-fold higher cardiovascular mortality than the general population [116]. GHRT helps maintaining normal bone density and body composition and decreases cardiovascular risks [117,118]. A recent consensus statement summarizing available evidence concludes that GHRT is safe in patients with craniopharyngioma [112].

In the case of frequently encountered tumour- and/or treatment-associated ACTH deficiency in craniopharyngioma patients, hydrocortisone substitution therapy and flexible dose-adaptation with regard to stress situations is mandatory [119]. Non-physiological over-replacement of hydrocortisone may promote the development of obesity. A well-balanced and adapted dosage of hydrocortisone is beneficial for stabilizing BMI and functional capacity as well as preventing risks of adrenal crisis and hypoglycaemia. Patient and parental training on the perception of stress situations and appropriate and rapid intervention in life-threatening emergency situations such as acute adrenal crisis is of vital importance [120].

Gonadotrophin deficiency may necessitate pubertal induction and medically assisted reproduction, which is often unsatisfactory, leading to impairment in intimate relationships, sexuality, and intimacy [70,71]. Not surprisingly, rates of sexual activity are lower and psychosexual dysfunction higher in adult patients treated during childhood [70,121].

Based on hypothalamic origin, oxytocin deficiency is likely in some craniopharyngioma patients with tumor- and/or treatment associated hypothalamic involvement leading to hypothalamic syndrome. Accordingly, decreased salivary concentrations of basal and/or stimulated oxytocin have been observed in craniopharyngioma patients [82,122-124] when compared with healthy controls. Reduced oxytocin levels were associated with anxiety [125] and worse social cognition [126]. Craniopharyngioma patients with anterior hypothalamic lesions were observed with lower oxytocin saliva levels and best neuropsychological response to a single nasal oxytocin administration [122,123], when compared with craniopharyngioma patients with posterior hypothalamic lesions and normal controls. The results

suggest that oxytocin-based therapeutics could be useful in treating craniopharyngioma patients with hypothalamic syndrome [76,127].

Psychosocial disorders

Craniopharyngioma patients may suffer from behavioral, psychosocial or psychiatric disorders, such as anxiety, impulse-control disorders, depression, apathy [124,128-130] or severe food craving behaviors requiring additional specific psychiatric and/or psychosocial support. Pharmacotherapeutic interventions with central stimulating agents, such as dextroamphetamines may help to decrease daytime sleepiness and increase concentration and may be considered to target psychosocial symptoms.

Quality of life

The spectrum of psychosocial function after craniopharyngioma ranges from excellent in the majority of patients to reduced functionality [80,124]. The most frequently reported impairments can be attributed to emotional and social function with reports of self-care deficits, psychopathological symptoms (depression, anxiety, apathy) [128], and impairments in everyday functioning (learning difficulties, unsatisfactory peer relationships, inability to control emotions and disturbed body image) [131]. Preoperative functional limitations and tumour characteristics, such as larger tumour volume, hypothalamic and 3rd ventricle involvement, can be identified as risk factors for impaired long-term QoL [80].

In addition, endocrine, neurological and ophthalmological sequelae impair QoL [5]. Common neurocognitive consequences of craniopharyngioma are cognitive problems, particularly those affecting executive function, attention, episodic memory and working memory [131,132]. Cognitive rehabilitation interventions (functional behavioural analysis and goal management therapy) can be efficient therapeutic options that compensate for psychosocial and neurocognitive challenges [133].

Update on therapies for management of the consequences of craniopharyngioma

The prognosis and QoL after craniopharyngioma can be improved by preventing or decreasing treatment-associated hypothalamic damage, thereby reducing morbidity and mortality rates [66,79,134-137]. Prevention of hypothalamic damage is frequently accomplished by limiting neurosurgical interventions with the use of novel imaging techniques, such as 7-Tesla MRI or through task-related functional MRI [138]. These techniques may help to better identify hypothalamic structures, guiding the neurosurgeon perioperatively to minimize hypothalamic damage.

Novel medications for treatment of hypothalamic obesity in craniopharyngioma patients have shown initial promising results (**Table 1**). After careful selection of patients, treatment may be aimed at reducing food intake and/or increasing resting energy expenditure, using pharmacological agents such as dextroamphetamines, oxytocin receptor agonists, ghrelin antagonists, or GLP-1 receptor agonists. For increasing activity of brown adipose tissue, atomoxetine a selective blocker of the presynaptic norepinephrine transporter may be used. First experiences with brown adipose tissue transplantation in an animal model show that energy expenditure can be increased by activating brown adipose tissue [139].

A randomized placebo-controlled study of 8 weeks intranasal oxytocin for children and young adults with tumour-induced hypothalamic obesity (NCT 02849743) is ongoing. While safety data so far are reassuring, neuropsychological effects of intranasal oxytocin on psychosocial behaviour and emotion regulation have been observed in craniopharyngioma patients [82,122,123]. Further well-powered clinical trials are warranted to analyse and understand the optimal drug formulation and dosing regimen.

Recently, *Tesomet,* a drug combining tesofensine with metoprolol, has been given the FDA orphan drug status for treating hypothalamic obesity. In a small, randomized controlled trial including 24 adults with hypothalamic obesity, *Tesomet* administered for 6 months was observed to reduce body

mass index with only mild and tolerable adverse effects. Further trials are warranted to proof tolerability and efficacy [89].

Deep brain stimulation (DBS) is a novel technique with potential benefit in the treatment of hypothalamic obesity after craniopharyngioma. DBS causes a 'functional' lesion or modulation of a brain network by high-frequency stimulation. Promising experiences have been reported for DBS in patients with epilepsy, dystonia, Parkinson's disease, and obsessive-compulsive disorders. First experiences in DBS treatment of eating disorders such as anorexia nervosa and obesity were promising. In three studies, DBS has been used for treatment of hypothalamic obesity in total six patients (five Prader-Willy Syndrome and one craniopharyngioma patient). Targets DBS included the nucleus accumbens (NAcc) and the lateral hypothalamic area (LHA). In the reported craniopharyngioma patient, NAcc-DBS lead to a decrease in BMI (-8.7%) [140]. No severe side effects have been observed in these trials.

Updates on Tumour Directed Management:

The management of craniopharyngioma remains predominantly surgery, with or without radiotherapy. However, as highlighted above, the consequences of tumour and therapies require a wider multidisciplinary team of medical and allied health professionals. In addition to advances in techniques and selection of patients for relevant surgery and radiotherapy approaches, novel targeted therapies are becoming increasingly used, particularly in management of PCP, but also now in ACP.

In deciding the optimal techniques for a given patient, careful balancing of tumour control against visual, endocrine, hypothalamic function and late effects requires nuanced discussion within the multidisciplinary team prior to initial surgery. It is increasingly appreciated this is best undertaken in centres with plenty of experience.

National and international groups are developing best practice recommendations, and the UK Children's Cancer and Leukaemia Group (CCLG) has provided a detailed evidence-based guideline, based on Delphi consensus, for management of children and young people (CYP) aged <19 years with craniopharyngioma (https://www.cclg.org.uk/guidelines/endocrine/craniopharyngioma). A European Reference Network guidance is also under development. In the next sections we give a brief overview and update of surgical, radiotherapy and medical management of tumours.

Surgery in craniopharyngioma

The continuing development of endoscopic operative techniques, intraoperative adjuncts, and understanding of the anatomical relationships between craniopharyngioma and adjacent anatomical structures substantially influence surgical management of this disease. These tools are increasingly employed with the overarching goal of maintaining the patients' quality of life over the long term. In order to best maintain this focus, preoperative multidisciplinary consultation that includes the neurosurgeon, neuro-oncologist, endocrinologist, radiation oncologist, ophthalmologist, and neuroradiologist is ideal. This should be pursued whenever it is feasible without placing the patient at short term risk. In the clear majority of patients with craniopharyngioma, there is ample time for preoperative multidisciplinary planning and discussion with the patient and family.

In this vein, it is critical for the neurosurgeon to possess at least a general understanding of the available therapeutic modalities for craniopharyngioma. Surgery and radiation therapy have been the foundation of treatment for these tumours for over 50 years. Improvements in technique and technology of both modalities influence their optimal application [110,141-144]. However, emerging medical antitumour therapies, discussed elsewhere in this review, may have a substantial impact on traditional algorithms regarding therapy for craniopharyngioma. Presently, this is especially true with regard to papillary craniopharyngioma (PCP) [145], but may also become relevant with regard to the adamantinomatous subtype (ACP) [29,39]. The availability of these therapies, when considered in

the context of craniopharyngioma as a chronic disease for which long term QoL considerations are paramount, allows for new and creative thinking around the selection of surgical therapy and the goals of a given intervention.

Goals of Surgery

Despite the evolving therapeutic context for craniopharyngioma, for any given operation, the patient/family and care team must still determine the goals of surgery. The first decision in this regard is whether gross total resection (GTR) is considered safe and feasible.

This decision remains controversial among neurosurgeons. There are often subjective factors, such as the comfort of the surgeon, age of the patient, or the preferences of the patient/family, which influence whether GTR is considered preferable. For example, younger patients have been reported to suffer more chronic life altering symptoms as a result of craniopharyngioma than older patients [111]. Therefore, these groups may merit different surgical strategies. In general, there is consensus around the priority to minimize the risk of damage to the hypothalamus. Multiple studies have demonstrated that poor quality of life correlates with hypothalamic dysfunction [111,146-148], whether iatrogenic or a direct result of tumour behaviour. Preservation of visual and pituitary function, when possible, as well as avoiding injury to critical skull base vasculature is also integral to decision making. While compression of the optic apparatus can often be relieved with surgical intervention, and pituitary hormones can be supplemented or replaced, hypothalamic dysfunction is not only life altering, but exceedingly difficult to treat [135,146,149-151]. However, given the more advanced developmental stage of the adult brain, in adult patients with CP, especially those with PCP or less cystic ACP – more aggressive surgery may be indicated [152].

Gross Total Resection (GTR)

Rates of recurrence following gross total resection without further anti-tumour therapy vary, and have been reported to range from 8% to 46% [110,153-156]. As such, complete surgical resection may be the simplest path to tumour cure. When a craniopharyngioma does not involve the hypothalamus, surgery with the goal of GTR is often preferred. This outcome can be achieved through various operative corridors, so each case merits individualized decision-making.

Subtotal Resection (STR)

Subtotal Resection is broadly defined as any operation that removes some volume of craniopharyngioma while leaving additional tumour *in situ*. There is no consensus volume or percentage of tumour that must be removed for a procedure to qualify as a STR. Following STR, additional antitumour therapy, most commonly radiation, is almost universally indicated. While the timing of this additional therapy may vary, it has been demonstrated that residual ACP is highly likely to grow within a relatively short interval if a strategy of watchful waiting is selected [154,156]. Nevertheless, there are contexts in which such a strategy is preferable. For example, in a young patient with a small volume of residual craniopharyngioma, the decision to closely monitor may allow the child to reach an age at which radiation is considered to be associated with less risk of developmental delay than it was at the age when the patient presented.

Cyst Fenestration

Among the challenges in the management of craniopharyngioma is the difference in behaviour between solid and cystic components of the tumour. While solid components often grow fairly slowly and are well controlled following radiation, cysts can move quickly and are much less reliably responsive to radiation therapy, especially within the first 12 months after therapy. It is therefore not uncommon for a tumour cyst to cause symptomatic mass effect in the absence of solid tumour growth. While medical therapies to control cyst growth may be emerging [39], current first line therapy

is operative cyst decompression/fenestration. The operative approach to cystic disease can be through any number of corridors, and requires individualized decision making.

One application of cyst fenestration that has been utilized with increasing frequency is trans-ventricular endoscopic wide fenestration [151,157-159]. This approach is effective for the control of monocystic disease in which the cyst extends into or fills the third ventricle, and results in obstructive hydrocephalus. Through a burr hole approach, hydrocephalus can be durably treated without placing indwelling hardware in most cases. If the fenestration is wide, the cyst very rarely recurs. This approach further affords the opportunity for cyst fluid sampling and definitive tissue biopsy with minimal risk of neurological injury. The surgeon is also offered direct visualization of the relationship between the tumour and the hypothalamus. This can offer critical information regarding whether GTR may be a feasible subsequent management goal. By treating obstructive hydrocephalus, this procedure may additionally create time for the care team to better assess the patient's neuroendocrine status and the tumours relationship to the hypothalamus. This aids in decision-making regarding further care [55]. GTR has been achieved through a trans-ventricular endoscopic approach[158], although in most cases this is not the goal.

Cyst Catheter Placement

Intracystic therapies are another tool for the management of cystic craniopharyngioma. The surgeon plays a critical role with regard to placement of the catheter within the cyst. This can be done under stereotactic or endoscopic guidance, or using direct vision. The position of a catheter within the cyst provides the opportunity for cyst fluid aspiration or delivery of intracystic therapies through an indwelling access device. While multiple different agents, including Bleomycin and radioisotopes, have been employed as intracystic therapeutics [160-165], the most common recently has been Interferon-α [160,162,166]. Multicentre international retrospective data indicate that this approach can help delay disease progression with a favourable risk profile [162]. This may be especially relevant

when considered in the context of craniopharyngioma as a chronic disease in young people. In addition, endoscopic cyst fenestration is not as reliable with regard to cyst decompression when the cyst is located in the subarachnoid space, rather than within the ventricle. As such, catheter placement for cysts in the subarachnoid space may be appropriate.

Surgical Corridor and Context

The selection of an operative corridor for the treatment of craniopharyngioma will frequently be influenced by the goals of surgery. Patient characteristics, including the presence of acute hydrocephalus, visual status, pituitary dysfunction, and midface size/patient age are also critical contributors. This again, emphasizes the concept that each patient merits an individualized approach that considers long term management.

Acute Surgical Intervention

Urgent or emergent operative intervention for craniopharyngioma is most frequently necessary for the management of obstructive hydrocephalus. While visual decline may be another indication, this more frequently results from chronic compression of the optic apparatus. Consistent with other causes of acute hydrocephalus, cerebrospinal fluid diversion can be rapidly achieved via external ventricular drain (EVD) placement or CSF shunting. When transventricular endoscopy and wide cyst fenestration is employed, an EVD is left in the ventricle at the conclusion of the procedure.

a. Tumor Directed Corridors

1. Transnasal Endoscopic

As a midline skull base tumor, craniopharyngioma is often anatomically amenable to a transnasal endoscopic approach (**Figure 3**). Among the advantages of this approach for resection of

craniopharyngiomas is the visualization of critical structures, such as the optic apparatus and carotid vasculature. Depending on the specific anatomy of the tumour and the pituitary function of the patient, the pituitary stalk and gland can be identified and preserved. The relationship between the tumour and the floor of the third ventricle can also be appreciated in detail, allowing for informed intraoperative decision-making with regard to the goals of surgery (e.g. pursuing GTR when the tumour drops easily from the floor of the third ventricle). In both paediatric and adult populations, this approach has increased in use over recent years [167-170], and in many centres this is the preferred operative corridor for craniopharyngioma. Data from paediatric centres demonstrate that, in experienced hands, this approach is safe and efficacious even in young patients [144,171,172].

2. Craniotomy

Craniotomy for resection of craniopharyngioma still represents the most established operative approach, having been developed prior to current endoscopic technologies. Open cranial approaches offer the benefit of wide visualization and control of tumour and perilesional structures. Multiple series demonstrate the safety and efficacy of open craniotomy for the resection of craniopharyngioma [143,155,173]. The most commonly used craniotomy is the pterional approach, which offers frontolateral skull base access to the suprasellar region (**Figure 4**). When compared to other open cranial approaches, the pterional approach offers a short distance to the tumour with a fairly wide angle for instrument movement. It can also be expanded to include an orbital osteotomy, which further increases exposure [174]. As this approach is often used for other indications, it is also familiar to most adult and paediatric neurosurgeons. As a lateral approach, the pterional craniotomy does have limitations with regard to identification of contralateral vascular structures. Identification of the relationship of the tumour to the floor of the 3rd ventricle and the superior hypophyseal vessels can also be limited.

A number of other open cranial approaches are commonly employed for the removal of craniopharyngioma. The midline subfrontal approach can be expanded by performing medial orbital osteotomies in order to maximize midline anterior skull base exposure. Alternatively, a less invasive eyebrow incision and small frontal craniotomy can provide subfrontal access to a craniopharyngioma [175-177]. For craniopharyngiomas that project superiorly, an anterior interhemispheric approach may be employed [178]. Tumours that project inferiorly, into the posterior cranial fossa, may be debulked using a suboccipital craniotomy.

3. Transventricular Endoscopy

As described above, transventricular endoscopy can be a leveraged as a less invasive (relative to transnasal endoscopy or open craniotomy) approach to control cystic craniopharyngioma, and to help assess the extent of hypothalamic involvement [55]. The goals of surgery are usually limited, although GTR has been described [158].

Radiotherapy for Craniopharyngioma

External beam radiotherapy is the most common modality used for craniopharyngioma after neurosurgical colleagues have intervened to provide the diagnosis, decompress a cyst, improve CSF flow or treat hydrocephalus. Modern radiotherapy involves one of two modalities, photon base radiotherapy which usually comes in the form of intensity modulation (IMRT) or volumetric arc therapy (VMAT). Proton therapy can also be used and has the advantage of decreasing the integral dose to the patient's brain due to its physical properties of lower entrance dose and elimination of exit dose compared with photon radiotherapy [3,179]. Doses to the tumour bed of 54 Gy (or Gy_{RBE} for proton radiotherapy) are typically used and control rates range from 70-80% at 5 years (Jimenez, 2021), with one series from St. Jude reporting 10-year disease control of 79% and 10 year overall survival of 96% [180]. A SEER analysis of both paediatric and adult craniopharyngioma patients found 5-

and 10- year overall survival rates to be 86% and 83%. In the SEER multivariate analysis, they found that younger age, smaller tumour size, white ethnicity and use of radiation therapy were the factors that remained significantly associated with better survival [181]. There is no difference in disease control between photon and proton modalities but since many patients are treated as children, the better sparing of radiation dose to surrounding normal brain can improve neurocognitive outcomes compared to photon techniques. Radiation dose to the nearby brain can impair development and result in a decline of neurocognitive functioning that is inversely correlated with age and directly correlated with dose and volume of brain irradiated. When a patient is very young, commonly the role of extirpative surgery is favoured to try to avoid the neurocognitive effects of radiation. However, the risk of an aggressive surgery and hypothalamic or vascular involvement should be weighed carefully against the risks of radiotherapy [182].

Cystic components of the craniopharyngioma that appear to be growing will often require either cyst fenestration, cyst resection or placement of a catheter and subcutaneous reservoir by the neurosurgery team (such as an Ommaya reservoir). Cyst fenestration may only temporarily relieve the pressure from the cyst. Complex cysts or cysts that seem to reaccumulate quickly should have a catheter and reservoir placed so that the cyst contents can be aspirated during radiotherapy. Keeping the total tumour/target volume as small as safely possible decreases the integral dose to the rest of the brain. Cysts that grow and do not have an easy means of aspiration or decompression require that the radiation oncologist obtains surveillance imaging and may need to replan the patient to ensure the cyst is encompassed in the radiation port [183]. The expediting of a craniopharyngioma patient to radiation due to the growing cyst usually is not terribly effective, as cysts typically continue to grow under treatment. Furthermore, cysts can continue to expand for up to a year after radiotherapy. Those that are located near the optic nerves or pressing on the brainstem may require surgical intervention or aspiration through a reservoir for several months after treatment. If a patient has a growing cyst that suggests impending CSF outflow obstruction or

visual impairment, then that cyst should be surgically addressed with resection of the cyst or reservoir placement.

Certain parts of the brain are more eloquent for higher cognitive functioning and include the temporal lobes and frontal lobes [184-186]. Typically, a 4-field approach is used for proton radiotherapy (see RT **Figure 5**) that attempts to relatively spare dose to the more eloquent regions of the brain, but tumour geometry and patient anatomy typically drive the beam choices with the goal of minimizing as much dose as possible to the supratentorial brain. VMAT or IMRT are excellent alternatives to proton radiotherapy which remains limited in availability in most parts of the world.

Radiotherapy should be delivered with interval imaging (every 1-2 weeks) with MRI or CT scan if CT can provide sufficient visualization of the cyst [180]. Cysts can differ in density on CT and some are well visualized and others are poorly visualized on CT. It is imperative that craniopharyngioma cysts be included within the radiation field to stop subsequent growth with time. In some cases, this will require replanning of the target volume to include growing cysts. For radiation therapy to be optimally effective for tumour control, large breaks in the radiation delivery should be avoided. Therefore, if a patient appears to be heading for a surgical intervention within the anticipated 6 weeks of radiotherapy deliver, that intervention should happen prior to the start of radiation [183,187].

Radiotherapy can be delivered either immediately after biopsy or sub-total surgical resection, or the patient can be observed for disease progression and radiotherapy can be instituted at the time of progression—although it is optimal to use radiation with smaller amounts of residual disease [181]. For any given patient, their clinical situation will have nuance that determines optimal management. Factors that will help steer clinical decision making include the solid and cystic components of the tumour, rate of growth, extent of resection, patient age, and co-morbidities. Usually, a multidisciplinary discussion about optimal management including the neurosurgeon, radiation oncologist, radiologist and paediatric oncologist is helpful to discussing the merits and trade-offs of the treatment approaches and timing of them [4,5].

The acute side effects of radiotherapy are usually mild and well tolerated but can include fatigue, hair loss in the treatment portal, nausea, vomiting and anorexia. These typically remit shortly after treatment ends. Late side effects of treatment can include hormonal deficits if the patient has not already suffered from endocrine deficiencies, effects on neurocognition that is age and volume related, and second tumour risks. Vasculopathy is possible from compression of the tumour of the vessels in the circle of Willis, but the addition of radiotherapy augments this risk further. Lucas et al. found a 48% risk of some vessel abnormality after definitive treatment, and 5% of whom required a revascularization procedure [188]. Usually, radiotherapy does not cause diabetes insipidus, but very commonly causes endocrine deficiencies in those patients not already rendered endocrine deficient from the tumour or the surgery. Onset of endocrine deficiency can be as early as six months after treatment and younger patients are at higher risk than older patients [189]. However, the dose to the hypothalamus and/or pituitary is usually more than 50 Gy give the suprasellar location of these tumours and thus all patients should be screened and followed for life for endocrine deficits. Cortisol deficiency can be life threatening if undiagnosed, but the other hormones can cause significant morbidity if unreplaced [187,189].

In summary, radiotherapy is often necessary to attain durable control of craniopharyngiomas and can be optimally employed with limited surgery to minimize adverse side effects of treatment. It is usually well tolerated and with modern techniques neurocognitive outcomes are improved and become hard to measure past the age of 12 [180]. However, patients remain at risk for endocrine deficits, and vasculopathies, and obesity and should be followed for decades so that early intervention can help maximize the quality and quantity of survivorship [2,179,189].

Medical therapies

A range of medical therapies has been tried over the years. Multiple different agents, including bleomycin and radioisotopes, have been employed as intracystic therapeutics [160-165]. Adverse effects associated with leakage into surrounding tissues has led to testing of safer alternatives. The most

common recently has been Interferon-α (IFNα) [160,162,166]. Multi-centre international retrospective data indicate that this approach can help delay disease progression with a favourable risk profile [162]. This may be especially relevant when considered in the context of craniopharyngioma as a chronic disease in young people. A recent trial has also evaluated the role of systemic administration of pegylated IFN in patients with progressive/relapsed disease with or without radiotherapy [190]. Partial response was observed in two of seven patients, who had not previously received radiotherapy, but only one had a sustained response for more than 3 months. None of 11th patients, who had been previously treated with radiotherapy, showed an objective response. Whilst the authors suggest the median progression free survival at 19.5 months was encouraging, it is likely that systemic IFNα has only a limited role in patient management.

Systemic administration of chemotherapy generally had no role in the management of craniopharyngioma [191]. It has been used in a subset of patients with aggressive disease and/or malignant histology, resulting in radiological response in some case reports [192,193].

In papillary craniopharyngioma, targeting of BRAF and MAPK pathway has increasingly been used in recent years [145,194-198]. Initially used within individuals with progressive/recurrent disease, a trial of combined BRAF/MEK inhibition using oral vemurafenib/cobimetinib in 28-day cycles in patients with BRAF alterations and no prior RT has provisionally reported responses in up to 93% of patients, with a median reduction in tumour size of -83% (range: -52% to -99%). Toxicity has been as expected with these agents, predominantly skin, fever, arthralgia/myalgia, increased liver enzymes &/or creatinine kinase. Children with PCP have also been treated with these agents, with some success [199]. In this case, rapid tumour regrowth occurred following discontinuation of the inhibitor highlighting the likely need to combine use of these agents with other treatment modalities. As experience accumulates and the final trial is published, it is likely that the duration and endpoint (e.g. to facilitate easier/less morbid definitive surgery) of administration of these agents in PCP will become better defined.

As discussed above, several targeted therapeutic agents have been suggested as potential beneficial in the treatment of ACP, including IL6 inhibitors, MAPK pathway inhibitors and immune checkpoint inhibitors, with patients treated with these agents via compassionate access. Several clinical trials, led by the CONNECT and PNOC clinical trial consortia are currently running to evaluate these agents in patients (ClinicalTrials.gov NCT05233397, NCT05286788, NCT05465174). Understanding the roles of these agents within well conducted clinical trials, with interrogation of biology of samples, will be essential in understanding their benefit. As highlighted by the preclinical studies of SHH inhibitors, the expression of a target alone is not sufficient to show benefit, and indeed has potential to cause harm and promote tumour growth. The rarity and heterogeneity in tumour characteristics (cyst, solid, etc) mean that these trials will require international co-operation and careful consideration of clinically relevant endpoints in order to lead to improvements in practice.

Conclusions

Considerable advance has been achieved in the understanding of the pathogenesis of craniopharyngioma. In the case of ACP, while the primary pathway driving tumour growth cannot presently be targeted, the discovery of other secondary pathways may offer new treatment modalities. In particular, inhibition of the MAPK pathway and interfering with IL6 signalling are promising candidates against these clinically aggressive tumours. This cautious optimism is supported by recently published results in a handful of patients with ACP, who showed significant responses upon treatment with either MAPK and IL6 inhibitors [29,39]. Although inflammation in ACP has been long considered to be an important player in the pathogenesis [34], functional characterisation has just started to be revealed. Of note, the effects of inflammatory mediators may be not just nearby tumour cells, but also in surrounding non-tumoural tissues. In fact, recent results support the notion that inflammation may contribute to function deterioration of the hypothalamus, pituitary gland and optic pathways [54]. It is becoming increasingly clear that a few non-proliferative, senescent cells within the tumours play a critical role in tumour growth and invasion [200]. Through the activation of a robust SASP, the paracrine actions of growth factors and inflammatory mediators

from senescent cells (e.g. β-catenin-accumulating cell clusters) create a protumourigenic microenvironment in both mouse and human ACP [37,200-202].

Craniopharyngiomas are morbid tumours and their treatment is perhaps even more so. Referral of craniopharyngioma patients to expert centres or treatment networks [203] is mandatory, where a multidisciplinary treatment group should develop the most optimal and risk-adapted management scheme aiming at (a) reversal of visual impairments, (b) normalization of increased intracranial pressure, (c) treatment of tumour progression, (d) substitution of pituitary endocrine deficiencies, and (e) minimizing acute and long-term mortality and morbidity with special regard to conserving integrity of hypothalamic structures. For craniopharyngioma patients with hypothalamic syndrome, novel treatment approaches are warranted, which should be evaluated in preferable international collaborative trials.

The tailored surgical component of craniopharyngioma management depends upon a surgical team that is able to select the most appropriate operative corridor and goals of surgery. To approach a goal of maximal safe resection, operative experience is ideally combined with an understanding of the available non-surgical management options within the context of the ultimate goal to maximize the patients quality of life over the long term. Improved surgical techniques include decreasing morbidity from the surgery itself, supplemented by a better understanding of which patients are more likely to benefit from other available therapies. Furthermore, the partnering of conservative surgery and cyst management with either resection or reservoir placement allows the radiation oncologist to keep the treatment volume to a minimum so as to improve late side effect profiles. Management of patients with craniopharyngioma is an effort that is best optimized with multidisciplinary input. The apparent success of medical therapies in PCP, and the emergence of multiple potential targeted therapies in ACP, offers opportunities to reconsider the management of the “most challenging of the intracranial tumours”.

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4

Figure Legends

Fig. 1. Histological features of human craniopharyngioma.

Top panel. Haematoxylin & eosin staining and immunohistochemistry against □-catenin on human ACP histological sections. Human ACPs are heterogenous tumours containing tumour epithelia (TE) and glial reactive tissue (GRT). Closer examination of the tumour epithelia identifies cells grouped in whorl-like structures (WL), which are surrounded by large cells with empty cytoplasm (stellate reticulum, SR) and a pseudostratified palisading epithelial layer (PE). Immunohistochemistry shows that nucleo-cytoplasmic accumulation of □-catenin occurs mostly in the whorl-like structures (WL).

Bottom panel. Haematoxylin & eosin staining and immunohistochemistry against BRAF-V600E of human PCP histological sections. Human PCPs contain large sheets of squamous epithelia (SE) surrounding by fibrovascular cores (FC), which provide support to the tumour cells. FCs are lined by a pseudostratified epithelium (PSE). Immunohistochemistry shows the expression of BRAF-V600E throughout the squamous epithelium, but not in the fibrovascular cores. Figure is adapted from Martinez-Barbera JP, Andoniadou CL (2020) Biological Behaviour of Craniopharyngiomas. Neuroendocrinology 1–8, with permission of S. Karger AG, Basel.

Figure 2. Model depicting the complex paracrine signalling within ACP and known targetable pathways.

Senescent beta-catenin accumulating senescent clusters secrete factors that activate autocrine and paracrine signalling pathways across a range of cell types both within the tumour and reactive tissue. The MAPK pathway is active within the palisading epithelium and reactive glia. A diverse inflammatory infiltrate includes a range of cell types, and may be modulated by pro-inflammatory stimuli, e.g. lipid, inflammatory mediators (e.g. cytokines) and immune checkpoints. The modulation of these signals may be of therapeutic benefit. Potential therapeutic drugs targeting specific pathways are highlighted.

Figure 3: Patient with craniopharyngioma amenable to transnasal endoscopic approach with a goal of gross total resection.

A. Sagittal Plane Computed Tomogram demonstrating remodeling and expansion of the sella turcica as a result of long-standing and slow tumour growth. **B.** Sagittal Plane T1-weighted MRI following gadolinium contrast administration demonstrating a bilobed cystic tumour filling the sphenoid sinus as well as the sella and suprasellar region with mass effect on the optic apparatus and abutting the third ventricle. **C.** Coronal Plane T2-weighted MRI demonstrating the same cystic tumour with a small solid component at the floor of the cyst. Note there is no dilation of the lateral ventricles. **D.** Intraoperative photo taken through a transnasally positioned endoscope following tumour resection. The inferior surface of the frontal lobe and Anterior Cerebral Arteries are well visualized, demonstrating one of the advantages of the transnasal endoscopic operative approach. **E.** Postoperative Sagittal Plane T1-weighted MRI following gadolinium contrast administration demonstrating tumour resection with an open suprasellar space and intact third ventricle floor. **F.** Postoperative Coronal Plane T2-weighted MRI demonstrating the same tumour resection.

Figure 4: Craniopharyngioma approached by pterional craniotomy in a patient with near normal pituitary function.

A. Sagittal Plane Computed Tomogram demonstrating a normal to small sella turcica with a small volume of tumor associated calcification at the dorsum sella. **B.** Sagittal Plane T1-weighted MRI following gadolinium contrast administration demonstrating a suprasellar craniopharyngioma with a normal appearing pituitary gland and abutment or involvement of the floor of the 3rd ventricle. **C.** Axial Plane T2-weighted MRI demonstrating the same tumor with a small cystic component that involves the wall of the 3rd ventricle. Again, there is no dilation of the lateral ventricles. These panels demonstrate a suboptimal corridor for a transnasal operative approach, especially when considered

in the context of the patient having near normal pituitary function, with only growth hormone deficiency. This tumor was therefore approached using a right pterional craniotomy **D.** Intraoperative photograph taken through the operating microscope. This demonstrates the optic chiasm (orange circle), tumor (yellow star) and right internal carotid artery (blue triangle). **E.** Postoperative Sagittal Plane T1-weighted MRI following gadolinium contrast administration demonstrating tumor resection with a small volume of contrast enhancing residual tumor (adjacent to star) that was intentionally left *in situ* when it was intraoperatively found to be very adherent to the 3rd ventricle **F.** Postoperative Axial Plane T2-weighted MRI demonstrating the same tumor resection, with a smaller cystic tumor remnant related to the walls of the 3rd ventricle (adjacent to star).

Figure 5. Representative proton radiation treatment plan and dose volume histograms demonstrating dose to critical normal structures that could impact development of late effects.

Top panel. This image shows the craniopharyngioma target volume in magenta. The isodose lines correspond to the dose level depicted at the side legend. The prescription dose is 54 Gy, but the chiasm is slightly underdosed since it was under pressure from the tumor and the patient has mild color vision deficits. Doses above 54 are not allowed in the chiasm or the brainstem. Dose to other normal structures (brain, temporal lobes, hippocampi and hypothalmus) are tracked by drawing these structures on the planning CT and MRI scans and calculating the dose to each. Four fields are used, a posterior field, a superior field and two lateral fields. The beam stops shortly after treating the target which results in a low integral dose to the brain**.**

Bottom panel. This represents the Dose-Volume Histogram, which is how radiation oncologists keep track of the dose to the normal structures as well as the target volume which is depicted here as CTV1 Suprasellar (CTV stands for clinical target volume).

Table 1: Recent reports on pharmacological treatment approaches for acquired, non-congenital hypothalamic obesity

Pharmacolo-gical agent	Mechanism of action	Patient cohorts	Outcomes	Authors
Dextro-amphetamine	Central stimulant, stimulation of noradrenalin, dopamine secretion and dopamine reuptake inhibition	4 CP (3 ped) 1 ped astrocytoma 1 ped ganglioglioma 1 ped meningitis	Reduction in continuous weight gain and stabilisation of BMI	Denzer et al.[83]
Methyl-phenidate	Central stimulant, dopamine reuptake inhibition	1 ped CP	Beneficial against weight gain	Elfers *et al.* [84]
Diazoxide and metformin	Reduced insulin secretion, reduced hyperglycaemia, improved insulin sensitivity	9 ped CP	Reduced weight gain, weight loss, peripheral edema, emesis, elevated hepatic enzymes	Hamilton *et al* .[85]
Exenatide	GLP-1 receptor agonists, improved insulin sensitivity, increased satiety feeling, reduced speed of gastric emptying	4 ped CP 1 ped germinoma	No significant weight loss in total cohort	van Schaik *et al.*[86]
		5 adult CP 1 ped hamartoma 1 adult astrocytoma 1 adult germinoma	Improved cardiovascular profile, improved metabolic profile, sustained weight reduction	Zoicas *et al.* [87]
Liraglutide		1 adult CP	BMI reduction from 41.8 to 35.3 after 8 months intervention	Zoicas *et al.* [87]
Oxytocin (Oxy) and naltraxone	Naltroxane (opiate antagonist) decreases appetite and poten-tiates anorexigenic oxy effects	1 ped CP	Improvement of hyperphagia and weight loss	Hsu *et al.* [88]
Tesomet (combination of tensofensine and metoprolol)	Tensofensine = Inhibitor of the presynaptic reuptake of the neurotransmitters nor-adrenaline, dopamine, and serotonin	24 adult aquired hypothalamic obesity (10 CP)	In a RCT: 6.3% BMI reduction after 24 weeks tesomet with mild and tolerable side effects	Huynh *et al.* [89]

RCT= randomized controlled trial, CP= craniopharyngioma; ped= paediatric; oxy= oxytocin;

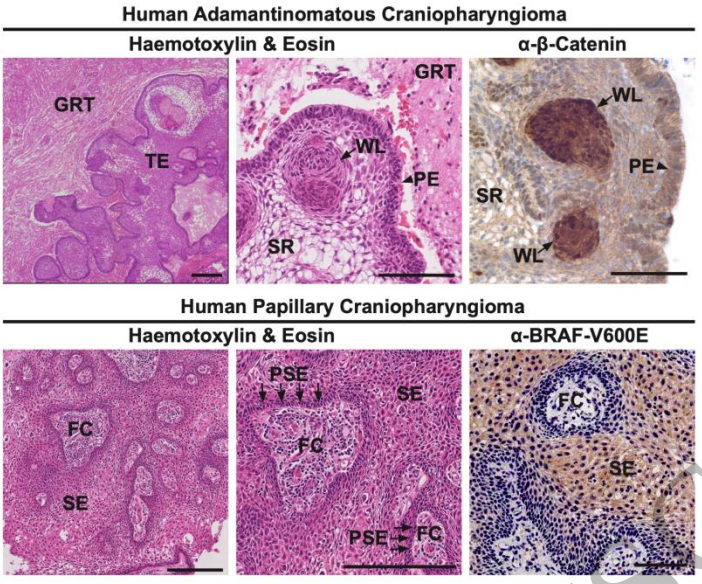

Figure 1

1

2 **Figure 1**
3 **559x314 mm (4.3 x DPI)**

4

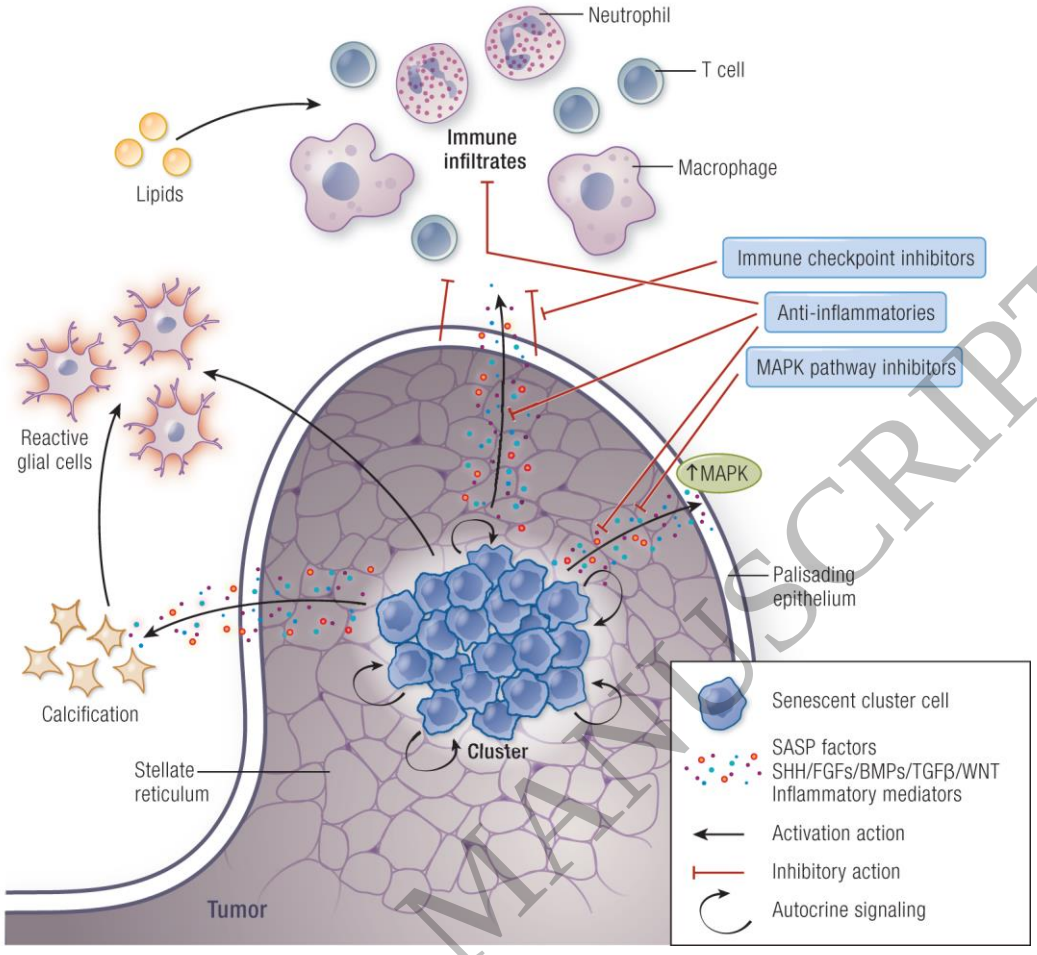

Figure 2
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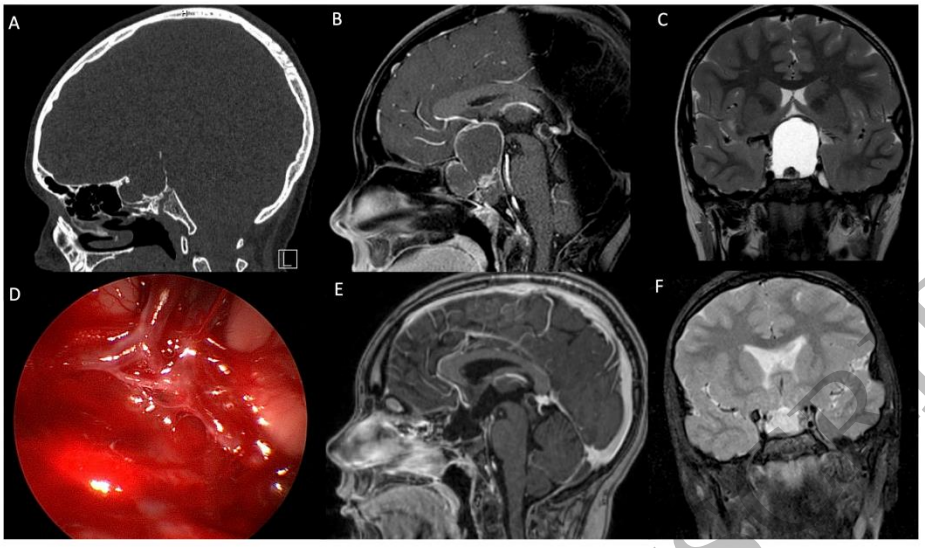


Figure 3

Figure 3
559x314 mm (4.3 x DPI)

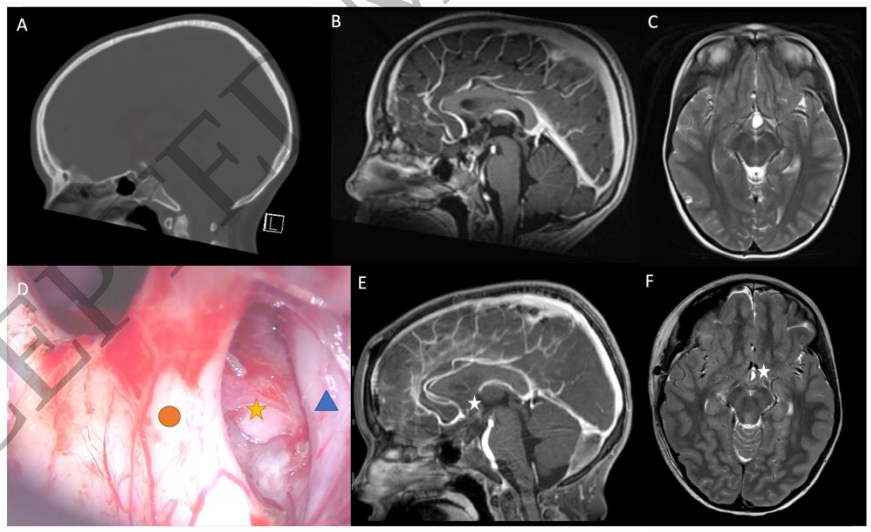


Figure 4

Figure 4
559x314 mm (4.3 x DPI)

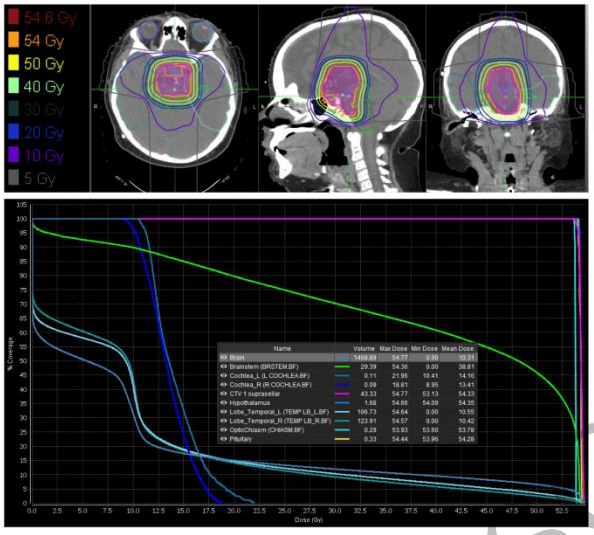
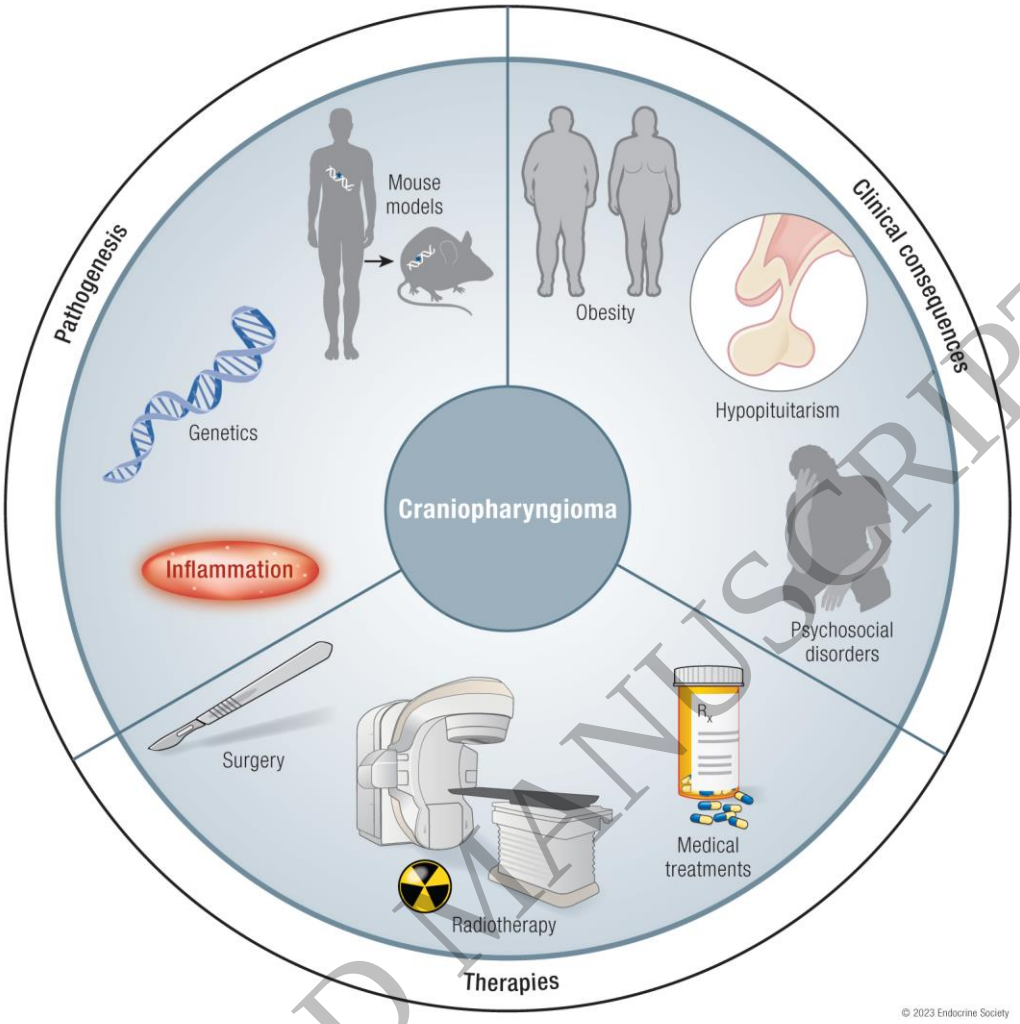


Figure 5.

Figure 5
559x314 mm (4.3 x DPI)



Graphical Abstract

Essential points:

- Adamantinomatous and papillary craniopharyngioma (ACP and PCP, respectively) are two tumour entities characterised by distinct pathology and genetics.

- Evidence is accumulating indicating that targeting the MAPK pathway in both tumour entities, and inhibiting IL6 signalling in ACP, may be of therapeutic value.

- To minimise the consequences of the tumours and of the therapies, on reducing quality of life, a wider multidisciplinary team of medical and allied health professionals is required.