National UK guidelines for the management of paediatric craniopharyngioma

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Summary

Although rare, craniopharyngiomas constitute up to 80% of tumours in the hypothalamo-pituitary region in childhood. Despite being benign[1], their location close to the visual pathways, hypothalamus and pituitary gland means that both tumour and treatment can cause significant long-term neuroendocrine morbidity on a background of high overall survival. To date, the optimal management strategy for these tumours remains undefined, with practice varying significantly between centres. In light of this, as part of a national endeavour to create evidence- and consensus-based guidance for the management of rare paediatric endocrine tumours in the United Kingdom, the following guideline was developed under the auspices of the UK Children's Cancer and Leukaemia Group (CCLG) and the British Society for Paediatric Endocrinology & Diabetes (BSPED), with the oversight and endorsement of the Royal College of Paediatrics and Child Health (RCPCH) using AGREE-II methodology in order to standardise care for children and young people with craniopharyngiomas.

Introduction

Craniopharyngiomas are rare, benign sellar and/ or suprasellar tumours accounting for up to 80% of paediatric tumours in this area[1–4]. Paediatric craniopharyngiomas are almost invariably adamantinomatous and histologically exhibit a combination of cystic, solid and calcified components[5,6]. Human and mouse models have demonstrated characteristic β-catenin (*CTNNB1*) mutations, WNT signalling pathway hyperactivation, over-expression of *SHH,* and β-catenin accumulation in cell clusters[7,8].

Diagnosis can be often delayed, with the most frequent presenting symptoms related to raised intracranial pressure, visual compromise, or hypothalamo-pituitary dysfunction[9–14]. 30-year survival rates are high (up to 80%[10,15]) but punctuated by multiple relapses and interventions, causing significant long-term morbidity. Management largely consists of neurosurgical resection and/ or radiotherapy but varies significantly, and the optimum strategy remains undefined[16].

Having recognised these challenges, as part of a UK-wide endeavour to generate evidence- and consensus-based guidelines for rare paediatric endocrine tumours, the Guideline Development Group (GDG) convened under the auspices of the Children's Cancer and Leukaemia Group (CCLG) and the British Society for Paediatric Endocrinology and Diabetes (BSPED), with the oversight and endorsement of the Royal College for Paediatrics and Child Health (RCPCH), to provide recommendations and standards of best practice for health professionals for the diagnosis, investigation, treatment and long-term follow-up of children and young people (CYP, defined as <19 years of age) with adamantinomatous craniopharyngiomas.

Methods

Clinical questions were agreed by the GDG prior to stakeholder endorsement. Literature searches of the Ovid MEDLINE (1946 – March 2020), Cochrane Library (including the Cochrane Database of Systematic Reviews (2016, Issue 12), Cochrane Central Register of Controlled Trials (CENTRAL, 2016, Issue 12), and Database of Abstracts and Reviews of Effect (DARE, 2015 Issue 1) electronic registries were conducted in November – December 2014, and subsequently repeated in February 2017, April 2019, March 2020 and May 2021, with no significant changes to any of the recommendations made.

Only articles published in English were included. Abstracts of studies identified were filtered to include only relevant studies pertaining to the diagnosis, investigation, management and follow-up of adamantinomatous craniopharyngiomas in CYP. The remaining studies were reviewed using the GRADE approach by GDG members working in pairs. 239 published primary studies (including case series and case reports) were reviewed, as well as 7 national or international evidence-based guidelines (Figure 1, Appendix page 15). Where there was insufficient evidence to make a recommendation, a proposed recommendation was taken forward to up to two Delphi consensus rounds, requiring >70% agreement for inclusion (Appendix page 11). Recommendations were classified as strong (1, “offer”), moderate (2, “consider”) or weak (3, “be aware”) and the quality of evidence as high (⊕⊕⊕⊕), moderate (⊕⊕⊕O), low (⊕⊕OO) or based on Delphi consensus (⊕OOO). Recommendations based on Delphi consensus alone did not preclude them being strong. When higher quality evidence was unlikely due to pre-existent extremely widespread clinic practice, the

GDG did not put these forward to the Delphi consensus process, making recommendations based on internal GDG consensus (recommendations 1.2, 2.2.1, 3.3.1 and 3.3.7).

The final guideline was circulated amongst stakeholders between December 2020 – July 2021 for final comments, and then peer reviewed by five independent reviewers (Appendix page 11). The RCPCH Quality Improvement Committee provided quality assurance throughout and endorsement of the final guideline.

Recommendations

Generic statements

1.1 Offer management in a specialist paediatric endocrine centre by an age-appropriate endocrinologist with experience in pituitary tumours, in liaison with the designated multidisciplinary neuro-oncology team to all children and young people <19 years of age (CYP) with a suspected or confirmed craniopharyngioma. (1| ⊕OOO)

1.2 Age-appropriate hypothalamo-pituitary multidisciplinary team (MDT) support (neurosurgery, paediatric oncology, radiation oncology, endocrinology, neuroradiology, neuropathology) including, where appropriate, adult pituitary specialists (e.g. endocrinologists and skull base neurosurgeons) should be provided. (1| ⊕⊕OO, GDG consensus recommendation)

1.3 Offer pituitary surgery performed in an age-appropriate specialist setting with on-site perioperative joint endocrine care to all CYP. (1| ⊕OOO)

1.4 Offer surgery by the neurosurgeon(s) nominated by the adult pituitary or paediatric neuro-oncology MDT, which can offer all possible approaches, including transsphenoidal, transcranial and endoscopic-assisted surgery. (1| ⊕OOO)

1.5 Offer discussion, where necessary, of complex sellar/ suprasellar lesions in CYP at a national pituitary tumour MDT for review of radiology, histology and decision-making. (1| ⊕OOO)

1.6 Offer continued lifelong care and transition to adult pituitary services, on an individualised basis, usually when growth and puberty are complete, to all CYP treated for craniopharyngiomas. (1| ⊕OOO)

1.7 Given the rarity and significant morbidity of pituitary tumours in CYP, a national clinical database should be created for monitoring outcomes to optimise care and prognosis in this patient group (1| ⊕OOO)

The above largely consensus-based recommendations were made as part of the overarching rare paediatric endocrine tumours guideline development project. One low-quality study showed that larger centres were less likely to undertake radical surgery with better quality of life outcomes[17]. Recommendation 1.2 was strengthened by GDG consensus as a recognition of best practice.

Diagnosis and investigations

2.1 <u>Radiology</u>

2.1.1 MRI with dedicated pituitary views in both sagittal and coronal planes (as per Children's Cancer and Leukaemia Group (CCLG) guidelines) should be the routine imaging modality in assessment of CYP with suspected craniopharyngioma, but

where the diagnosis and/ extent of calcification is in doubt, consider additional CT scanning. (1| ⊕⊕OO, GDG consensus recommendation)

2.1.2 Be aware of the option of performing diffusion tensor imaging (DTI), perfusion-weighted imaging (PWI) and magnetic resonance spectroscopy (MRS), although these are not routinely recommended in the pre-operative assessment of craniopharyngiomas in CYP and have no clear proven role. (3| ⊕OOO)

2.1.3 The pre-operative MRI report should include grading of the extent of hypothalamic involvement according to the system defined by Puget et al. (2007). *(1| ⊕⊕⊕⊕)*

Other lesions in this area do not generally show a combination of cystic, solid, and calcified components. MRI can delineate tumour extent but CT scanning is more sensitive in detecting calcification (55-95% of craniopharyngiomas), and should be performed whenever the diagnosis is in doubt or to determine the extent of resection[5,6]. MRI sequences should be in keeping with CCLG guidelines for imaging paediatric brain tumours[18]. Pre-operative grading of hypothalamic involvement to inform hypothalamic-sparing surgery should be performed. Utilisation of the most replicated grading system by Puget et al. (2007)10, decreases the risk of adipsia, hyperphagia and obesity[11,19–22]:

- Grade 0 – no hypothalamic involvement
- Grade 1 – tumour abutting or displacing the hypothalamus
- Grade 2 – hypothalamus not identifiable separately from the tumour.

2.2 <u>Vision</u>

2.2.1 Offer visual acuity, visual fields and fundoscopy before treatment in all cooperative CYP. Consider pattern visual evoked potentials in infants of disabled children but these should not be used for surveillance in the longer-term. (1| ⊕⊕OO, GDG consensus recommendation)

2.2.2 Be aware of optical coherence tomography (OCT) as a method of assessing retinal nerve fibre layer thinning in CYP with more severe degrees of visual acuity or field loss. (3| ⊕⊕OO)

Visual function needs to be assessed by an array of methods in children with a range of visuo-cognitive development. Age-standardised visual acuity remains most important in guiding treatment decisions[23,24], whilst the presence of visual symptoms (particularly in CYP <6 years of age), optic atrophy or papilloedema correlates with poorer visual outcomes[25–27]. OCT may be useful in patients where standard assessments may not be possible.

2.3 Endocrinology

2.3.1 Offer baseline plasma endocrine biochemistry in all CYP at presentation of suspected craniopharyngioma which should include urgently analysed AFP, β-hCG and prolactin available before any definitive surgery; as well as IGF-1, TSH, free T_4, LH, FSH, testosterone/ oestradiol, paired early morning plasma/ urine osmolalities and electrolytes, and, if no dexamethasone has been instituted, a morning cortisol +/- ACTH. (1| ⊕OOO)

2.3.2 Be aware that a random cortisol measurement taken before administration of any dexamethasone may be useful in documenting pre-treatment status of the hypothalamo-pituitary-adrenal axis in CYP presenting acutely with raised intracranial pressure. In the absence of treatment with dexamethasone for peri-

tumoral oedema, be aware that morning cortisol concentrations +/- ACTH may also be measured prior to any prophylactic steroid cover. (3| ⊕⊕OO)

2.3.3 In the non-acute situation, offer combined dynamic pituitary function tests of growth hormone and cortisol reserve, and, if age-appropriate, gonadotrophin secretion when feasible and before any steroid therapy when possible. (1| ⊕OOO)

2.3.4 Be aware that deteriorating serial thyroid function tests (low or normal TSH concentrations with repeatedly low/ borderline low/ falling free T_4 concentrations at least 1-2 weeks apart) are sufficient for diagnosis of central hypothyroidism, without the need for a TRH test which does not adequately discriminate between hypothalamic and pituitary causes of thyroid dysfunction. (3| ⊕⊕OO)

2.3.5 Be aware that a formal water deprivation test may help confirm central diabetes insipidus (CDI) in CYP with a known suprasellar tumour and a history of polydipsia and/ or polyuria where other metabolic causes have been excluded, but in the absence of an inappropriately dilute polyuria with plasma hyperosmolality (urine: plasma osmolality ratio <1.0), especially if the posterior pituitary bright spot is absent on MRI. (3| ⊕⊕OO)

2.3.6 Be aware of the presence of the hypothalamic syndrome and the possibility of performing a formal psychological assessment at diagnosis. (3| ⊕⊕OO)

80-90% of CYP with craniopharyngiomas have hypothalamo-pituitary deficits at diagnosis, with GH deficiency being the commonest (75-81%), followed by deficiencies in LH/ FSH (40-50%), TSH (25-37%), ACTH (22-25%), and CDI (7-31%)[9,19,28]. Basal prolactin, AFP and β-hCG should be performed to exclude the diagnoses of prolactinoma and secreting germ cell tumour respectively. Basal and where feasible, dynamic pituitary function tests should be conducted prior to treatment.

Assessment of GH secretion should follow GH Research Society recommendations[29]. The gold standard insulin tolerance test may be substituted by the standard synacthen test (sensitivity 77-91%, positive predictive value 97-99%)[30,31] to determine adrenal status. Central hypothyroidism should be defined by the presence of a low or normal TSH with repeatedly low or falling (by >20%) free T_4 concentrations[32].

In children with polyuria and polydipsia a water deprivation test may not always be necessary, and may in fact be hazardous[33]. Coexisting CDI may not manifest until glucocorticoid replacement has commenced. Plasma copeptin measurements may be useful for diagnosing CDI (baseline cut off <3.5 pmol/l sensitivity 75-100%, specificity 83-87%)[34,35].

More recently, a novel score for the assessment of hypothalamic syndrome has been published showing that >50% of patients with suprasellar lesions such as craniopharyngiomas and low-grade gliomas had elements of hypothalamic dysfunction[36].

2.4 Neuropsychology

2.4.1 Offer all CYP with craniopharyngioma a baseline neurocognitive assessment around the time of diagnosis against which to monitor future progress. (1| ⊕OOO)

There are no data on neurocognitive deficits in CYP with craniopharyngiomas at presentation. A baseline assessment was strongly recommended by Delphi consensus.

2.5 Pathology

2.5.1 Except in occasional surgical emergencies, offer delayed definitive surgical or radiotherapeutic treatment until confirmatory pre- or perioperative tissue histopathology or cyst fluid cytology is available. (1| ⊕OOO)

2.5.2 Be aware that Ki67 labelling or CTNNB1 mutation analysis of tissue have poor prognostic value. (3| ⊕⊕OO)

Where possible a histological diagnosis should be obtained prior to definitive treatment, unless appearances are clearly typical intraoperatively or in neurosurgical emergencies. No molecular markers correlate with overall (OS) or progression-free survival (PFS) and therefore need not be measured routinely[37–41].

Treatment

3.1 Surgery

3.1.1 Be aware that access to a surgeon with specific experience in paediatric craniopharyngioma surgery may improve overall outcomes. (3| ⊕⊕OO)

Studies evaluating the effect of neurosurgical experience on outcomes were of low quality in small patient cohorts[42–45]. One survey of members of the American Society of Paediatric Neurosurgeons demonstrated a significant difference in outcomes and mortality according to neurosurgical experience, but suffered significant selection bias[44].

3.1.2 Consider surgery (complete or subtotal resection or cyst aspiration) given the better overall and progression-free survival compared with conservative management alone. (2| ⊕⊕⊕O)

3.1.3 Consider not proceeding with complete resection of paediatric craniopharyngiomas where there is clear evidence of hypothalamic involvement on Paris grading. (2| ⊕⊕⊕O)

Several large retrospective cohort studies and meta-analyses suggest that gross total resection (GTR) results in better OS and PFS than subtotal resection (STR) alone, the latter resulting in poor local control rates and potentially increasing the risk of visual deterioration[10,46–49]. However, the latter can be “rescued” with adjuvant radiotherapy (GTR 5-year PFS 77% vs STR + radiotherapy 5-year PFS 73%) without the increased risk of long-term morbidity and CDI, particularly in tumours with hypothalamic involvement[15,46,48–51]. Given the indirect evidence that CDI and ACTH deficiency are associated with late mortality[28,52], the pre-operative hypothalamic grading is important in determining the overall surgical treatment strategy.

3.1.4 Be aware of the spectrum of options available for surgical management of hydrocephalus, including but not limited to insertion of ventriculo-peritoneal (VP) shunts, external ventricular drains, transventricular endoscopic cyst drainage, transsphenoidal endoscopic cyst drainage or insertion of an Ommaya reservoir into a craniopharyngioma cyst, tailoring these to each patient. (3| ⊕⊕OO)

3.1.5 Be aware of the option of using solely primary cyst drainage to treat hydrocephalus due to a craniopharyngioma cyst, rather than ventriculo-peritoneal shunt or external ventricular drain insertion. (3| ⊕OOO)

3.1.6 Be aware of the option of transventricular or transsphenoidal cyst drainage with/ without insertion of an Ommaya reservoir to control cyst size in cystic craniopharyngiomas. (3| ⊕⊕OO)

3.1.7 Be aware of the option of a two-staged surgical approach involving minimally invasive surgery, relief of hydrocephalus and intracranial pressure, further neuroradiological assessment and MDT discussion before any definitive surgery of large mixed cystic/ solid craniopharyngiomas with/ without hydrocephalus. (3| ⊕⊕OO)

3.1.8 Be aware of the option of using high-field intraoperative MRI although this may not improve outcomes of craniopharyngioma surgery. (3| ⊕⊕OO)

There are multiple methods of managing hydrocephalus and craniopharyngioma cysts, and it is important that patients can access a full range of these techniques[53–55]. A staged surgical approach is suggested[56–58], particularly in cystic craniopharyngiomas causing hydrocephalus, where cyst decompression should precede the insertion of shunts and/ or reservoirs. Evidence for the usefulness of intraoperative MRI has been limited to surgical case reports and case series[59,60].

3.2 Perioperative management

3.2.1 Offer CYP with cerebral oedema and those undergoing craniotomy or wide opening of the cerebrospinal fluid space transsphenoidally rapidly tapered perioperative (48-72 hours) dexamethasone neuroprotection. (1| ⊕OOO)

The widespread practice of perioperative dexamethasone to reduce peritumoral oedema has been used for several decades, with low quality evidence showing it reduces post-neurosurgical mortality[61]. Two adult studies suggest it is likely overused – withholding steroids in pituitary adenoma surgery results in no increased risk of complications[62], whilst tapering dexamethasone more rapidly does not increase neurological morbidity whilst reducing the risk of hypertension[63]. However, there is an

absence of evidence in paediatric practice and the recommendation above was therefore made by Delphi consensus.

3.2.2 Be aware that perioperative hydrocortisone at stress doses could be given without dexamethasone cover. If commenced, consider tapering post-operatively to maintenance doses until integrity of the hypothalamo-pituitary-adrenal axis has been established. (3| ⊕⊕OO)

A meta-analysis of routine peri-operative hydrocortisone in adult pituitary adenoma surgery found insufficient evidence to support this practice but reported a low prevalence of post-operative adrenal insufficiency (1.0-12.9%)[64]. Adult pituitary tumour surgery guidelines recommend peri-operative hydrocortisone cover for at least 48 hours in cases where selective adenomectomy is not possible[65]. Given that certainty around intraoperative pituitary function is unlikely in craniopharyngioma surgery, the GDG suggests that CYP not receiving dexamethasone (recommendation 3.2.1) should routinely receive pre-operative stress doses of hydrocortisone, continued until post-operative evaluation of the hypothalamo-pituitary-adrenal axes. Dosing should be in line with BSPED, Society for Endocrinology, the Association of Anaesthetists and the Royal College of Physicians consensus guidelines[66,67].

Patients with proven intact pre-operative adrenal function and small pituitary masses undergoing non-resective surgery (e.g. VP shunt insertion), may discontinue hydrocortisone 24-48 hours post-operatively with monitoring of morning serum cortisol and ACTH concentrations.

3.2.3 Be aware of the diagnosis of CDI (which may progress to a triphasic response), iatrogenic intravenous hyperhydration, glycosuria, and/ or cerebral salt-wasting syndrome in the presence of post-operative polyuria. (3| ⊕⊕OO)

3.2.4 Be aware of the diagnosis of central adrenal insufficiency, the syndrome of inappropriate antidiuretic hormone (SIADH) secretion (possibly as part of a triphasic response), iatrogenic water overload and/ or cerebral salt-wasting syndrome in the presence of post-operative hyponatraemia. (3| ⊕⊕OO)

Management of post-operative salt-water balance requires specialist paediatric endocrinology input. The use of vasopressin receptor antagonists (tolvaptan) is not routinely recommended in view of the risk of masking and/ or worsening the post-operative triphasic response. This well-documented phenomenon, where CDI occurs in the first 24-48 hours, followed by SIADH in the first 1-2 weeks, followed by permanent CDI is more likely in paediatric patients[68]. Cerebral salt-wasting syndrome can occur concurrently during any of the three phases[69,70]. This rare diagnosis is thought to be driven by atrial and brain natriuretic peptides[71,72], and is treated with salt replacement, with occasional use of mineralocorticoid administration (fludrocortisone). Plasma copeptin concentrations are often difficult to interpret with rapidly changing post-operative biochemistry.

3.3 Radiotherapy

3.3.1 Offer deferment of adjuvant radiotherapy where the surgical impression of complete resection has been confirmed on post-operative MRI and/ or CT. (1| ⊕⊕OO, GDG consensus recommendation)

3.3.2 Consider upfront external beam radiotherapy where tumour resection is incomplete. (2| ⊕⊕⊕O)

3.3.3 Offer deferment of radiation until tumour progression is evident on a case-by-case basis where the MDT considers that the morbidity of radiation may outweigh its benefits in very young children or those with minimal residual disease. (1| ⊕OOO)

Upfront adjuvant radiotherapy post-GTR confers no additional benefit[10,48,73], and the GDG strengthened this recommendation on the basis of widespread practice such that further randomised control trials in this context are unlikely. Contrastingly, two systematic reviews have demonstrated that radiotherapy in the context of STR leads to similar 5-year PFS compared to GTR (67-77% vs 69-73%)[46,74]. The optimum timing of radiotherapy (upfront adjuvant vs. salvage) remains undetermined, with low quality evidence suggesting that salvage radiotherapy increases the risk of visual and endocrine morbidities, including CDI, without reducing survival[75,76]. However, there is a known risk to cognition in administering radiotherapy to young children, and the Delphi consensus panel agreed that radiotherapy can be delayed in selected cases.

3.3.4 Offer radiotherapy using the gross tumour volume (GTV) defined as the dimensions of the post-operative solid and cystic tumour complex. (1| ⊕OOO)

3.3.5 Offer radiotherapy using the clinical target volume (CTV) margin defined as 5 mm modified to barriers of natural spread. (1| ⊕OOO)

The GTV field should include the entire tumour bed, adjusted for the residual post-operative tumour volume[77,78]. A non-randomised study showed that reducing CTV margins from 10 to 5 mm does not reduce survival rates (88.1% vs. 96.2%)[77]. The above recommendations were strengthened by Delphi panel consensus.

3.3.6 Offer radiotherapy using a dose fractionation of 50.4-54 Gy (or equivalent CGE for proton beam therapy) administered in 28-30 fractions over 6 weeks to the planning target volume (PTV). (1| ⊕OOO)

No randomised control trials compare the various radiotherapy regimens used in craniopharyngiomas, ranging from total doses of 50-54 Gy in 28-30 fractions[77,79–81]. Some low-quality evidence suggests that doses of <54 Gy are associated with increased recurrence, but this needs to be balanced against the risk of radiotoxicity to the optic chiasm[82]. Regular cone beam CT or verification MRI should be performed to ensure that any cystic progression is adequately covered by the treatment plan. Replanning may be required if coverage is not adequate.

3.3.7 Consider high-energy proton beam therapy (PBT) as a radiation treatment modality. (2| ⊕⊕OO, GDG consensus recommendation)

PBT is increasingly becoming the radiotherapy modality of choice in brain tumours including craniopharyngiomas[83,84], due to a postulated reduction in risk of irradiating healthy brain tissue, and thus the risk of cognitive deficits[85], despite a lack of randomised control trials comparing long-term outcomes to conventional radiotherapy. Retrospective studies indicate no difference in OS or PFS[76], but one systematic review was equivocal about its use[86]. With increasing experience there has been recent concern that brainstem necrosis may be more frequent[87,88], but evidence for this being a PBT-specific effect rather than a radiation effect is unclear.

3.3.8 Be aware that gamma knife radiosurgery should only be considered as a primary treatment within a research setting as there is currently insufficient evidence for its efficacy. (3| ⊕⊕OO)

Stereotactic (gamma knife) radiosurgery (SRS) delivers a single, large radiation dose of 12-14 Gy to a small volume with high precision. Unlike in adults, there is no good quality evidence comparing SRS to other treatment modalities in children[89–91].

3.4 Other therapies

3.4.1 Be aware that intracystic chemotherapies should only be considered as a primary treatment within a research setting as there is currently insufficient evidence for its efficacy. (3| ⊕⊕OO)

No high-volume studies of intracystic chemotherapies compare outcomes with sham cyst aspirations or saline controls. Interferon-α (IFNα) is increasingly used in monocystic disease in light of the lower risk of neurotoxicity from leakage compared to bleomycin or radioisotopes, but there is insufficient evidence to recommend this as first-line[92–95]. At the time of publication there is a lack of availability of IFNα available worldwide. Studies have shown patients usually require further surgical resection, i.e., it only delays more definitive treatment[93]. Comparatively, intracystic bleomycin[96], intracystic radioisotopes (e.g. ^{32}P, ^{90}Y, ^{186}Re)[97–100] and systemic IFNα[101,102] are not well supported as a primary treatment strategy.

Post-treatment follow-up

4.1 Be aware that a follow-up MRI within 3-6 months of treatment may be needed to assess response. (1| ⊕⊕OO)

4.2 Offer MRI surveillance imaging at intervals guided by patient symptoms, definitive therapy (i.e. degree of resection and/ or radiotherapy), and by the MDT. (1| ⊕OOO)

There are no set protocols for the frequency of post-treatment serial imaging. Changes in tumour volume can occur between 3 months – 5 years post-radiotherapy[103,104].

Radiotherapy can also cause cyst expansion prior to shrinkage which may not always require intervention. Commonly, post-operative neuroimaging is performed at 48-72 hours, followed by early 3-month imaging and then 3-6 monthly thereafter in line with PBT trial protocols. More recently, the Response Assessment in Paediatric Neuro-Oncology (RAPNO) Working Group have released guidance recommending that the initial post-operative MRI should be performed within 2 weeks after surgical intervention[105].

4.3 Offer repeat formal visual acuity and, if age-appropriate, visual field assessment within 3 months of definitive tumour treatment. (1| ⊕OOO)

4.4 Offer ongoing visual follow-up at a frequency individualised according to age, residual visual function, symptoms, and likelihood of tumour/ cyst regrowth. (1| ⊕OOO)

Visual function usually only recovers after the first post-operative month[106,107], with visual outcomes being poorer in younger children with visual deficits at diagnosis[26,27]. However, no evidence exists for the optimum visual surveillance protocol and its accuracy for detecting recurrence. As such the above statements were agreed upon by Delphi consensus.

4.5 Offer basal and combined dynamic anterior pituitary function tests off any replacement therapy within 6 weeks of completion of initial treatment to assess the integrity of the GH, ACTH, TSH and, if age-appropriate, gonadotrophin axes, if not already found definitively abnormal at diagnosis. (1| ⊕OOO)

4.6 Consider using dynamic function testing as per local guidelines on several occasions over time to differentiate long-term recovery from dexamethasone-induced ACTH suppression from permanent ACTH deficiency. (1| ⊕OOO)

4.7 Offer lifelong endocrinology follow-up for evolving hypopituitarism, with the frequency determined on an individual patient basis. (1| ⊕OOO)

There is an overwhelming consensus that lifelong endocrine follow-up is required, including transition to specialist adult neuroendocrine services. The evolution of new hypothalamo-pituitary deficits is more common than their recovery over time, apart from ACTH and TSH deficiencies, the latter possibly due to adrenal suppression[9,10,28,108]. Serial reassessment of the hypothalamo-pituitary-adrenal axis may be required even many years later. Persistent CDI is more common in patients undergoing radical resection, recurrent operations, transcranial surgery and with pituitary stalk injury[68,109,110].

4.8 Consider recombinant human growth hormone (rhGH) in replacement doses in CYP with confirmed GH deficiency to re-establish normal linear growth, as this does not increase the risk of tumour progression. (2| ⊕⊕⊕O)

A range of retrospective studies show no evidence that rhGH treatment in replacement doses independently increases the background brain tumour relapse rate[111,112], including specifically in patients with craniopharyngiomas[47,113–115], or who are post-radiotherapy[116,117].

The optimum timing of when to start rhGH replacement is undetermined, and only the American Lawrence-Wilkins Paediatric Endocrine Society and Endocrine Society specifically suggest that in the case of craniopharyngiomas, there is no need to wait 1

year after end of treatment[118]. Prompt re-establishment of normal linear growth and limiting obesity, with appropriate rhGH dose titration should be considered one of the aims of endocrine management in survivors.

4.9 Consider access to a designated MDT with specialist dietary, exercise, psychological and endocrine input for the management of hypothalamic obesity. (2| ⊕⊕⊕O)

The pathophysiology of hypothalamic obesity is complex with no single effective intervention. A wide variety of treatment strategies have been used, including triiodothyronine[119], octreotide[120], dextroamphetamine[121], methylphenidate[122], sibutramine[123], and GLP-1 receptor agonists[124], mostly in small case series with short periods of follow-up, and not without adverse reactions. Bariatric surgery can result in weight loss and a reduction in type 2 diabetes[125]. However, there are significant risks in CYP with morbid obesity and life-threatening hypopituitarism, particularly as some procedures can cause malabsorption of oral hormone replacement medications. The longevity of weight loss also appears to reduce with time. Ultimately preventative neurosurgical strategies to limit hypothalamic damage and timely hormone replacement are cornerstones in management.

4.10 Be aware of specialist sleep laboratory and behavioural neuropsychopharmacology services for CYP with hypothalamic injury and disturbed sleep and/ or behaviour. (3| ⊕⊕OO)

12% of children are affected after surgery for craniopharyngiomas, with problems including sleep disordered breathing, sleep fragmentation, reduced sleep efficiency, sleep onset latency and obstructive sleep apnoea, particularly in those with

hypothalamic obesity and a history of previous radiotherapy[126–132]. Treatments such as modafinil, methylphenidate, dextroamphetamine and melatonin have been tried with variable effect[129,132–134]. Referral to specialist sleep laboratories is recommended.

4.11 Offer interval neuropsychological assessments until adulthood to inform clinical and educational neurorehabilitation and vocation in CYP with identified neuropsychology and neurological deficits, and those who have undergone cranial radiotherapy. (1| ⊕OOO)

A large quantity of literature describes the wide variety of neurocognitive deficits faced by CYP survivors, including decreased scores for general intelligence[135], visuospatial cognition[136], memory[135,137,138], executive function[139], and emotion and behaviour[140]. Some studies suggest that conservative surgical procedures with radiotherapy reduce the risk of neurocognitive impairment[141–143], whilst others directly link radiotherapy to behavioural and social impairments[144,145]. Systematic comprehensive longitudinal assessment of psychological and neuropsychological function is thus necessary in order to ensure survivors are able to access individualised and timely educational support, but there is no evidence for which patients should be prioritised, or the ideal method(s) of assessment.

Management of recurrence

5.1 Offer further surgery to avoid or reduce the radiation field before radiotherapy in CYP with cystic and/ or solid recurrences after a radiologically complete resection without previous irradiation. (1| ⊕OOO)

5.2 Offer further cyst drainage before radiotherapy in CYP with progressive, primarily cystic recurrences following initial incomplete resection without previous irradiation. (1| ⊕OOO)

5.3 Offer radiotherapy with further surgery to reduce the radiation field in CYP with progressive, primarily solid recurrences following initial incomplete resection without previous irradiation. (1| ⊕OOO)

5.4 Offer a repeat course of conventional radiotherapy for the treatment of disease progression or recurrence after previous irradiation only in exceptional cases and only after all other therapeutic modalities have been explored, given its high morbidity. (1| ⊕OOO)

The management of recurrent or progressive craniopharyngiomas remains a significant challenge and no high-quality evidence supports any treatment strategy. The timing of radiotherapy does not affect survival outcomes (Recommendation 3.3.3)[75,76]. Second recurrence is more likely if radiotherapy is omitted from second line treatment[146,147]. The size of the cystic component of craniopharyngiomas can affect the radiotherapeutic response, and the Delphi consensus agreed that primarily cystic progressions should be aspirated before irradiation to the whole tumour volume. Similarly, surgery can be considered to reduce the radiation field in solid progressions, although a second procedure can be more difficult. A second course of radiotherapy requires very careful MDT consideration, due to the risk of re-irradiating the optic chiasm, surrounding vascular structures, and the developing brain[148,149].

5.5 Be aware that gamma knife radiosurgery for recurrent or progressive craniopharyngiomas should only be considered in a research setting. (3| ⊕⊕OO)

Similar to the evidence for the use of SRS as primary treatment, no high quality paediatric evidence supports the use of SRS in recurrent or progressive craniopharyngiomas. One study consisting of a mixed cohort of adults and children showed similar 5-year PFS after SRS and STR with adjuvant radiotherapy (83% vs. 80%); both being better than STR alone (16%)[146]. Some data suggest that SRS has a favourable risk profile for small tumours (<1.6 cm^3) away from the optic pathway[89,150,151].

5.6 Be aware that repeated courses of intracystic interferon-α (IFNα) via an indwelling catheter could be considered instead of aspiration alone for recurrent cystic craniopharyngiomas. (3| ⊕⊕OO)

Published outcomes on the use of intracystic IFNα in the literature are difficult to separate from its use as part of primary treatment strategies (Recommendation 3.4.1)[92–94]. As such its use in progressive or recurrent craniopharyngiomas in CYP should not be recommended as routine.

5.7 Be aware that systemic IFNα should only be considered in a research setting. (3| ⊕⊕OO)

IFNα-2a or pegylated IFNα-2b has been reportedly effective in patients with cystic recurrence or progression[101,102,152]. However, there are significant side effects including pyrexia, neutropenia, transaminitis, fatigue, rashes, seizures, insomnia and anxiety[102], which needs to be considered carefully in a cohort with hypopituitarism and potential ACTH deficiency. Systemic IFNα should therefore not be administered to CYP outside the context of a clinical trial.

Conclusion

This guideline sets out evidence- and consensus-based standards for best practice in the management of these rare paediatric tumours. It also identifies a lack of high-quality evidence relating to this age group and the need for CYP with craniopharyngiomas to be managed in a multidisciplinary setting, with access to national expertise, in conjunction with patients and their families to be able to weigh the risks and benefits of the various treatment options available. Lastly, it highlights the gaps in current evidence underpinning current management strategies, including the long-term outcomes of proton beam therapy, the optimum timing of radiotherapy, the efficacy of intracystic therapies, the management of tumour progression, and the treatment of hypothalamic dysfunction.

Author contributions

H.A.S. conceptualised the overarching project for the development of national guidelines for rare paediatric endocrine tumours, led the overarching scoping exercise in collaboration with the CCLG, and acquired funds for this project. H.W.G. and P.M. performed the literature searches and the initial identification of potentially relevant references. H.W.G. wrote the initial draft of this manuscript.. All authors (H.W.G., P.M., A.A., K.A., C.C., Y.C.C., E.D., S.F., T.J., M.K., A.K., J.L., L.R., I.S., N.Thom., S.T., N.Thor., F.V.K., D.W., B.Z., C.M., H.A.S.) were responsible for the formulation of clinical questions for the literature searches, final literature review using the GRADE approach, formulation of Delphi statements, framing of recommendations and reviewing the final draft of this manuscript prior to submission.

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Conflicts of interest

- H.W.G. has received a one-off consulting fee from Rhythm Pharmaceuticals for development of a drug for hypothalamic obesity (not listed in manuscript, not licensed for indication for this indication currently).
- B.Z. has received honoraria from Medtronic for delivering lectures on electromagnetic neuronavigation and equipment and financial support to run the annual International Endoscopy in Neurosurgery course.
- H.A.S. is the voluntary chair and founder of the SUCCESS Charity.

Role of the funding source

All listed sources of financial contributions were paid solely to cover travel expenses, meeting room hire, facilitate administrative organisation and printing costs.
This required co-ordination of up to 150 professionals nationwide providing input into a large project to provide 8 management guidelines for rare paediatric endocrine tumours. Other published guidelines include those for pituitary stalk thickening (Cerbone M *et al.*; Lancet Child Adolesc Health 2021; 5:662-676) and differentiated thyroid carcinoma (Howard S *et al*.; Endocr Relat Cancer 2022; 29:G1-G33).

Some (£6,000) limited pump-priming funds were provided in 2013 by the two professional (BSPED and CCLG) societies who commissioned all 8 of these collaborative guidelines to be produced to the national NICE AGREE-II standard endorsed by the Royal College of Paediatrics and Child Health (RCPCH).
In 2016 these required supplementing with contributions from other charities and Sandoz pharmaceuticals as detailed below. Funding was channelled through SUCCESS Charity (a subfund of UCLH Hospitals Charity) to the CCLG and earmarked for this project where they now feature on their website (https://www.cclg.org.uk/professionals/rare-endocrine-tumour-guidelines).

This subfund has since closed and the residual funds were transferred in 2020 to the now national SUCCESS charity founded and still chaired voluntarily by Dr Helen Spoudeas to advocate for childhood brain tumour survivors (https://www.successcharity.org.uk/) where these guidelines are also publicised and freely available to all for best practice.

- CCLG £3000
- BSPED £3000
- British Society of Neurosurgeons £1000
- The Pituitary Foundation £1000
- SUCCESS Charity £2000
- The Association for Multiple Endocrine Neoplasia Disorders (AMEND) £3000
- Sandoz Pharmaceuticals £16000

Sandoz Pharmaceuticals was not part of the stakeholder membership and was not involved in any stage of the development of this guideline.

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Figure legends

Figure 1: Literature review process