National UK guidelines for the management of paediatric craniopharyngioma

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Although rare, craniopharyngiomas constitute up to 80% of tumours in the hypothalamic–pituitary region in childhood. Despite being benign, the close proximity of these tumours to the visual pathways, hypothalamus, and pituitary gland means that both treatment of the tumour and the tumour itself can cause pronounced long-term neuroendocrine morbidity against a background of high overall survival. To date, the optimal management strategy for these tumours remains undefined, with practice varying between centres. In light of these discrepancies, as part of a national endeavour to create evidence-based and consensus-based guidance for the management of rare paediatric endocrine tumours in the UK, we aimed to develop guidelines, which are presented in this Review. These guidelines were developed under the auspices of the UK Children's Cancer and Leukaemia Group and the British Society for Paediatric Endocrinology and Diabetes, with the oversight and endorsement of the Royal College of Paediatrics and Child Health using Appraisal of Guidelines for Research & Evaluation II methodology to standardise care for children and young people with craniopharyngiomas.

Introduction

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

Diagnosis of craniopharyngiomas is often delayed due to their slow growth rate and consequently insidious onset of non-specific symptoms, which are most frequently related to raised intracranial pressure, visual compromise, or hypothalamic–pituitary dysfunction.[9–14] 30-year survival rates are high (up to 80%),[10,15] but punctuated by multiple relapses and interventions, causing substantial long-term morbidity. Management largely consists of neurosurgical resection, radiotherapy, or a combination of the two approaches, but the optimum strategy remains undefined.[16]

Having recognised these challenges, as part of a UK-wide endeavour to generate evidence-based and consensus-based guidelines for rare paediatric endocrine tumours, the Guideline Development Group was assembled. This group convened under the auspices of the Children's Cancer and Leukaemia Group and the British Society for Paediatric Endocrinology and Diabetes, with oversight and endorsement of the Royal College for Paediatrics and Child Health, 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 (defined as <19 years of age) with adamantinomatous craniopharyngiomas.

Methods

Clinical questions were agreed by the Guideline Development Group before stakeholder endorsement. Literature searches of the Ovid MEDLINE (from database inception–March 1, 2020), Cochrane Library (including the Cochrane Database of Systematic Reviews (2016, issue 12), Cochrane Central Register of Controlled Trials (2016, issue 12), and Database of Abstracts and Reviews of Effect (2015, issue 1) electronic registries were conducted from Nov 21–Dec 23, 2014, and subsequently repeated in February, 2017, April, 2019, March, 2020, and May, 2021, with no major 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 children and young people. The remaining studies were reviewed using the Grading of Recommendations, Assessment, Development, and Evaluations approach by Guideline Development Group members working in pairs. 239 published primary studies (including case series and case reports) were reviewed, as well as seven national or international evidence-based guidelines (figure; appendix p 16). Where there was insufficient evidence to make a recommendation, a proposed recommendation was taken forward to up to two Delphi consensus rounds, requiring agreement of 70% or greater for inclusion (appendix p 249). Recommendations were classified as strong (1, offer), moderate (2, consider), or weak (3, be aware) and the quality of evidence as high, moderate, low, or based on Delphi consensus. 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 Guideline Development

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See Online for appendix

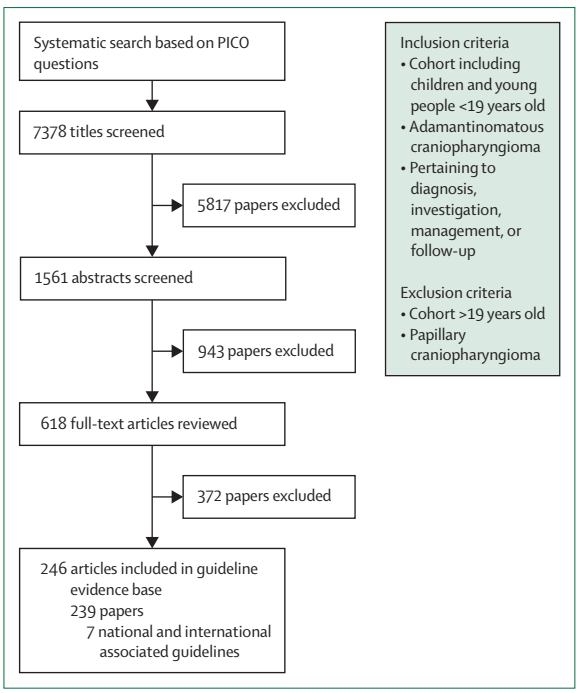


Figure: **Literature review process**

Group did not put this forward to the Delphi consensus process, making recommendations instead based on internal Guideline Development Group consensus (recommendations 1.2, 2.2.1, 3.3.1, and 3.3.7).

The final guideline was circulated among stakeholders between Dec 2, 2020 and July 22, 2021, and then peer reviewed by five independent reviewers (appendix p 12). The Royal College of Paediatrics and Child Health 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 under 19 years of age with a suspected or confirmed craniopharyngioma (recommendation: strong; evidence: based on Delphi consensus).

1.2 Age-appropriate hypothalamic–pituitary multidisciplinary team support (neurosurgery, paediatric oncology, radiation oncology, endocrinology, neuroradiology, and neuropathology) including, where appropriate, adult pituitary specialists (eg, endocrinologists and skull base neurosurgeons) should be provided (Guideline Development Group consensus recommendation; recommendation: strong; evidence: low).

1.3 Offer pituitary surgery performed in an age-appropriate specialist setting with onsite perioperative joint endocrine care to all children and young people (recommendation: strong; evidence: based on Delphi consensus).

1.4 Offer surgery by the neurosurgeon(s) nominated by the adult pituitary or paediatric neuro-oncology multidisciplinary team, which can offer all possible approaches, including transsphenoidal, transcranial, and endoscopic-assisted surgery (recommendation: strong; evidence: based on Delphi consensus).

1.5 Offer discussion, where necessary, of complex sellar and suprasellar lesions in children and young people with a national pituitary tumour multidisciplinary team for review of radiology, histology, and decision making (recommendation: strong; evidence: based on Delphi consensus).

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 children and young people treated for craniopharyngiomas (recommendation: strong; evidence: based on Delphi consensus).

1.7 Given the rarity and substantial morbidity of pituitary tumours in children and young people, a national clinical database should be created for monitoring outcomes to optimise care and prognosis in this patient group (recommendation: strong; evidence: based on Delphi consensus).

These 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 do radical surgery with better quality of life outcomes.[17] Recommendation 1.2 was strengthened by the Guideline Development Group consensus as a recognition of best practice.

Diagnosis and investigations

2.1 Radiology

2.1.1 MRI with dedicated pituitary views in both sagittal and coronal planes (as per Children's Cancer and Leukaemia Group guidelines) should be the routine imaging modality in assessment of children and young people with suspected craniopharyngioma, but where the diagnosis or extent of calcification is in doubt, consider additional CT scanning (Guideline Development Group consensus recommendation; recommendation: strong; evidence: low).

2.1.2 Be aware of the option of performing diffusion tensor imaging, perfusion-weighted imaging, and magnetic resonance spectroscopy, although these are not routinely recommended in the preoperative assessment of craniopharyngiomas in children

and young people and have no clear proven role (recommendation: weak; evidence: based on Delphi consensus).

2.1.3 The preoperative MRI report should include grading of the extent of hypothalamic involvement (recommendation: strong; evidence: high).[11]

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 have calcification), 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 Children's Cancer and Leukaemia Group guidelines for imaging paediatric brain tumours.[18] Preoperative grading of hypothalamic involvement to inform hypothalamic-sparing surgery should be performed. Use of the most replicated grading system[11] decreases the risk of adipsia, hyperphagia, and obesity.[19–22] Grade 0 indicates no hypothalamic involvement; Grade 1 indicates the tumour abutting or displacing the hypothalamus; and Grade 2 indicates that the hypothalamus is not identifiable separately from the tumour.

2.2 Vision

2.2.1 Offer visual acuity testing, visual fields testing, and fundoscopy before treatment in all cooperative children and young people. Consider pattern visual evoked potentials in infants or children with disabilities but these should not be used for surveillance in the longer-term. (Guideline Development Group consensus recommendation; recommendation: strong; evidence: low)

2.2.2 Be aware of optical coherence tomography (OCT) as a method of assessing retinal nerve fibre layer thinning in children and young people with more severe degrees of visual acuity or field loss (recommendation: weak; evidence: based on Delphi consensus).

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

2.3 Endocrinology

2.3.1 Offer baseline plasma endocrine biochemistry in all children and young people at presentation with suspected craniopharyngioma that should include urgently analysed α-fetoprotein (AFP), β-human chorionic gonadotropin (β-hCG), and prolactin available before any definitive surgery, as well as insulin-like growth factor 1, thyroid-stimulating hormone (TSH), free thyroxine (FT_4), luteinising hormone, follicle-stimulating hormone (FSH), testosterone, and oestradiol, paired early morning plasma and urine osmolalities and electrolytes, and, if no dexamethasone has been given, tests to evaluate morning levels of cortisol and adrenocorticotropic hormone (ACTH) (recommendation: strong; evidence: based on Delphi consensus).

2.3.2 Be aware that a random cortisol measurement taken before administration of any dexamethasone might be useful in documenting pretreatment status of the hypothalamic–pituitary–adrenal axis in children and young people presenting acutely with raised intracranial pressure. In the absence of treatment with dexamethasone for peritumoral oedema, be aware that morning concentrations of cortisol and ACTH might also be measured before any prophylactic steroid cover (recommendation: weak; evidence: low).

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 (recommendation: strong; evidence: based on Delphi consensus).

2.3.4 Be aware that deteriorating serial thyroid function tests (low or normal TSH concentrations with repeatedly low, borderline low, or falling FT4 concentrations at least 1–2 weeks apart) are sufficient for diagnosis of central hypothyroidism, without the need for a thyrotropin releasing hormone test that does not adequately discriminate between hypothalamic and pituitary causes of thyroid dysfunction (recommendation: weak; evidence: low).

2.3.5 Be aware that a formal water deprivation test might help to confirm central diabetes insipidus in children and young people with a known suprasellar tumour and a history of polydipsia or polyuria where other metabolic causes have been excluded, and in the absence of an inappropriately dilute polyuria with plasma hyperosmolality (urine to plasma osmolality ratio <1·0), especially if the posterior pituitary bright spot is absent on MRI (recommendation: weak; evidence: low).

2.3.6 Be aware of the presence of hypothalamic syndrome and the possibility of performing a formal psychological assessment at diagnosis (recommendation: weak; evidence: low).

80–90% of children and young people with craniopharyngiomas have hypothalamic–pituitary deficits at diagnosis, with growth hormone deficiency being the most common (75–81%), followed by deficiencies in

luteinising hormone and FSH (40–50%), TSH (25–37%), ACTH (22–25%), and central diabetes insipidus (7–31%).[9,19,28] Basal prolactin, AFP, and β-hCG testing should be performed to exclude the diagnoses of prolactinoma and secreting germ cell tumour. Basal and, where feasible, dynamic pituitary function tests should be conducted before any treatment is given. Assessment of growth hormone secretion should follow Growth Hormone Research Society recommendations.[29] The gold standard insulin tolerance test might 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%) FT_4 concentrations.[32] In children with polyuria and polydipsia, a water deprivation test might not always be necessary and could be hazardous.[33] Coexisting central diabetes insipidus might not manifest until glucocorticoid replacement has commenced. Plasma copeptin measurements can be useful for diagnosing central diabetes insipidus (baseline cutoff <3·5 pmol/l sensitivity 75–100%, specificity 83–87%).[34,35] A novel score for the assessment of hypothalamic syndrome has been published showing that more than 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 children and young people with craniopharyngioma a baseline neurocognitive assessment around the time of diagnosis to monitor future progress against (recommendation: strong; evidence: based on Delphi consensus).

To our knowledge, there are currently no data on neurocognitive deficits in children and young people with craniopharyngiomas. 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 preoperative or perioperative tissue histopathology or cyst fluid cytology is available (recommendation: strong; evidence: based on Delphi consensus).

2.5.2 Be aware that Ki67 labelling and CTNNB1 mutation analysis of tissue have poor prognostic value (recommendation: weak; evidence: low).

Where possible, a histological diagnosis should be obtained before definitive treatment unless appearances are clearly typical intraoperatively or in neurosurgical emergencies. Molecular markers that correlate with overall survival or progression-free survival have not been identified and therefore do not need to 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 might improve overall outcomes (recommendation: weak; evidence: low).

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 showed a significant difference in outcomes and mortality according to neurosurgical experience but had substantial 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 (recommendation: moderate; evidence: moderate).

3.1.3 Consider not proceeding with complete resection of paediatric craniopharyngiomas where there is clear evidence of hypothalamic involvement on grading (recommendation: moderate; evidence: moderate).

Several large retrospective cohort studies and meta-analyses suggest that gross total resection results in better overall survival and progression-free survival than subtotal resection alone, with subtotal resection resulting in poor local control rates and potentially increasing the risk of visual deterioration.[10,46–49] However, subtotal resection can be salvaged with adjuvant radiotherapy (gross total resection 5-year progression-free survival 77% *vs* subtotal resection plus radiotherapy 5-year progression-free survival 73%) without the increased risk of long-term morbidity and central diabetes insipidus, particularly in tumours with hypothalamic involvement.[15,46,48–51] Given the indirect evidence that central diabetes insipidus and ACTH deficiency are associated with late mortality,[28,52] preoperative 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 ventricular–peritoneal 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 (recommendation: weak; evidence: low).

3.1.5 Be aware of the option of using solely primary cyst drainage to treat hydrocephalus due to a craniopharyngioma cyst, rather than ventricular–peritoneal shunt or external ventricular drain insertion (recommendation: weak; evidence: based on Delphi consensus).

3.1.6 Be aware of the option of transventricular or transsphenoidal cyst drainage with optional insertion of an Ommaya reservoir to control cyst size in cystic craniopharyngiomas (recommendation: weak; evidence: low).

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 multidisciplinary team discussion before any definitive surgery on large mixed cystic or solid craniopharyngiomas with or without hydrocephalus (recommendation: weak; evidence: low).

3.1.8 Be aware of the option of using high-field intraoperative MRI, although intraoperative imaging might not improve outcomes of craniopharyngioma surgery (recommendation: weak; evidence: low).

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 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 children and young people with cerebral oedema and those undergoing craniotomy or wide opening of the cerebrospinal fluid space transsphenoidally rapidly tapered perioperative (48–72 h) dexamethasone neuroprotection (recommendation: strong; evidence: based on Delphi consensus).

The widespread practice of perioperative dexamethasone to reduce peritumoural oedema has been used for several decades, with low-quality evidence showing the practice reduces post-neurosurgical mortality.[61] Two adult studies suggest perioperative dexamethasone is likely overused—one study showed that withholding steroids in pituitary adenoma surgery resulted in no increased risk of complications;[62] another study showed that tapering dexamethasone more rapidly compared with a longer tapering regimen did not increase neurological morbidity while reducing the risk of hypertension.[63] However, there is an absence of evidence of the use of perioperative dexamethasone in paediatric practice and therefore recommendation 3.2.1 was 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 postoperatively to maintenance doses until integrity of the hypothalamic–pituitary–adrenal axis has been established (recommendation: weak; evidence: low).

A meta-analysis of routine perioperative hydrocortisone treatment in adult pituitary adenoma surgery found insufficient evidence to support this practice but reported a low prevalence of postoperative adrenal insufficiency (1·0–12·9%).[64] Adult pituitary tumour surgery guidelines recommend perioperative hydrocortisone cover for at least 48 h in cases where selective adenomectomy is not possible.[65] Given that certainty around intraoperative pituitary function is unlikely in craniopharyngioma surgery, the Guideline Development Group suggests that children and young people not receiving dexamethasone (recommendation 3.2.1) should routinely receive preoperative stress doses of hydrocortisone, continued until postoperative evaluation of the hypothalamic–pituitary–adrenal axis. Dosing should be in line with the British Society for Paediatric Endocrinology and Diabetes, Society for Endocrinology, Association of Anaesthetists, and Royal College of Physicians consensus guidelines.[66,67] Patients with proven intact preoperative adrenal function and small pituitary masses undergoing non-resective surgery (eg, ventricular–peritoneal shunt insertion), can discontinue hydrocortisone 24–48 h postoperatively, with monitoring of morning serum cortisol and ACTH concentrations.

3.2.3 Be aware of the diagnosis of central diabetes insipidus (which might progress to a triphasic response), iatrogenic intravenous hyperhydration, glycosuria, and cerebral salt-wasting syndrome in the presence of postoperative polyuria (recommendation: weak; evidence: low).

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 cerebral salt-wasting syndrome in the presence of postoperative hyponatraemia (recommendation: weak; evidence: low).

Management of postoperative 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 or worsening the postoperative triphasic response. This well-documented occurrence, in which central diabetes insipidus occurs in the first 24–48 h, followed by SIADH in the first 1–2 weeks, followed by permanent central diabetes insipidus, 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 postoperative biochemistry.

3.3 Radiotherapy

3.3.1 Offer deferral of adjuvant radiotherapy where the surgical impression of complete resection has been confirmed on postoperative imaging (eg, MRI or CT) (Guideline Development Group consensus recommendation; recommendation: strong; evidence: low).

3.3.2 Consider upfront external beam radiotherapy where tumour resection is incomplete (recommendation: moderate; evidence: moderate).

3.3.3 Offer deferral of radiation until tumour progression is evident on a case-by-case basis where the multidisciplinary team considers that the morbidity of radiation might outweigh its benefits in very young children or those with minimal residual disease (recommendation: strong; evidence: based on Delphi consensus).

Upfront adjuvant radiotherapy after gross total resection confers no additional benefit,[10,48,73] and the Guideline Development Group 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 shown that radiotherapy in the context of subtotal resection leads to similar 5-year progression-free survival compared with gross total resection (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 central diabetes insipidus, 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, defined as the dimensions of the postoperative solid and cystic tumour complex (recommendation: strong; evidence: based on Delphi consensus).

3.3.5 Offer radiotherapy using the clinical target volume margin, defined as 5 mm modified to barriers of natural spread (recommendation: strong; evidence: based on Delphi consensus).

The gross tumour volume field should include the entire tumour bed, adjusted for the residual postoperative tumour volume.[77,78] A non-randomised study showed that reducing clinical target volume margins from 10 mm to 5 mm does not reduce survival rates (88·1% *vs* 96·2%).[77] Recommendations 3.3.4 and 3.3.5 were strengthened by Delphi panel consensus.

3.3.6 Offer radiotherapy using a dose fractionation of 50·4–54·0 Gy (or equivalent cobalt gray equivalent for proton beam therapy) administered in 28–30 fractions over 6 weeks to the planning target volume (recommendation: strong; evidence: based on Delphi consensus).

To our knowledge, no randomised control trials have compared 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 less than 54 Gy are associated with increased recurrence, but this dosage 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 might be required if coverage is not adequate.

3.3.7 Consider high-energy proton beam therapy as a radiation treatment modality. (Guideline Development Group consensus recommendation; recommendation: moderate; evidence: low).

Proton beam therapy is increasingly becoming the radiotherapy modality of choice in brain tumours, including craniopharyngiomas.[83,84] This therapy is selected due to a postulated reduction in risk of irradiating healthy brain tissue, and thus the risk of cognitive deficits,[85] despite an absence of randomised controlled trials comparing long-term outcomes with conventional radiotherapy. Retrospective studies indicate no difference in overall survival or progression-free survival for proton beam therapy versus conventional photon therapy,[76] but one systematic review was equivocal about the use of proton beam therapy.[86] With increasing use of proton beam therapy there has been concern that brainstem necrosis might be more frequent,[87,88] but evidence for this being a proton beam therapy-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 (recommendation: weak; evidence: low).

Stereotactic (gamma knife) radiosurgery 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 stereotactic radiosurgery 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 efficacy (recommendation: weak; evidence: low).

No high-volume studies of intracystic chemotherapies compare outcomes with sham cyst aspirations or saline controls. Interferon alfa-2b (IFNα) is increasingly used in monocystic disease in light of the lower risk of neurotoxicity from leakage compared with bleomycin or radioisotopes, but there is insufficient evidence to recommend IFNα as a first-line treatment option.[92–95] At the time of publication, there is an absence of IFNα available worldwide. Studies have shown patients usually require further surgical resection (ie, IFNα therapy only delays more definitive treatment).[93] Comparatively, intracystic bleomycin,[96] intracystic radioisotopes (eg ^{32}P,^{90}Y,^{186}Re)[97–100] and systemic IFNα[101,102] are not well supported as primary treatment strategies.

Post-treatment follow-up

4.1 Be aware that a follow-up MRI within 3–6 months of treatment might be needed to assess response (recommendation: weak; evidence: low).

4.2 Offer MRI surveillance imaging at intervals guided by patient symptoms, definitive therapy (eg, degree of resection or radiotherapy), and by the multidisciplinary team (recommendation: strong; evidence: based on Delphi consensus).

There are no set protocols for the frequency of post-treatment serial imaging. Changes in tumour volume can occur between 3 months and 5 years post-radiotherapy.[103,104] Radiotherapy can also cause cyst expansion before shrinkage that might not always require intervention. Commonly, postoperative neuroimaging is performed at 48–72 h, followed by early 3-month imaging, and then 3–6 monthly thereafter in line with proton beam therapy trial protocols. The Response Assessment in Paediatric Neuro-Oncology Working Group have released guidance recommending that the initial postoperative 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 (recommendation: strong; evidence: based on Delphi consensus).

4.4 Offer ongoing visual follow-up at a frequency individualised according to age, residual visual function, symptoms, and likelihood of tumour or cyst regrowth (recommendation: strong; evidence: based on Delphi consensus).

Visual function usually only recovers after the first postoperative 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 the accuracy of such a protocol for detecting recurrence. As such, recommendations 4.3 and 4.4 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 growth hormone, ACTH, TSH, and, if age-appropriate, gonadotrophin axes, if not already found definitively abnormal at diagnosis (recommendation: strong; evidence: based on Delphi consensus).

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 due to permanent ACTH deficiency (recommendation: moderate; evidence: based on Delphi consensus).

4.7 Offer lifelong endocrinology follow-up for evolving hypopituitarism, with the frequency determined on an individual patient basis (recommendation: strong; evidence: based on Delphi consensus).

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

4.8 Consider recombinant human growth hormone in replacement doses in children and young people with confirmed growth hormone deficiency to re-establish normal linear growth, as this treatment does not increase the risk of tumour progression (recommendation: moderate; evidence: moderate).

A range of retrospective studies show no evidence that recombinant human growth hormone 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 have undergone radiotherapy.[116,117] The optimum timing to start recombinant human growth hormone replacement is undetermined, and only the American Lawrence-Wilkins Paediatric Endocrine Society and the Endocrine Society specifically suggest that in the case of craniopharyngiomas, there is no need to wait for 1 year after the end of treatment.[118] Prompt re-establishment of normal linear growth and limiting obesity with appropriate recombinant human growth hormone dose titration should be considered one of the aims of endocrine management in patients with craniopharyngiomas.

4.9 Consider access to a designated multidisciplinary team with specialist dietary, exercise, psychological, and endocrine input for the management of hypothalamic obesity (recommendation: moderate; evidence: moderate).

The pathophysiology of hypothalamic obesity is complex with no single effective intervention. Various 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, with reported adverse reactions. Bariatric surgery can result in weight loss and remission of type 2 diabetes.[125] However, there are substantial risks in children and young people 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, preventive neurosurgical strategies to limit hypothalamic damage and timely hormone replacement are cornerstones in management of hypothalamic obesity.

4.10 Be aware of specialist sleep laboratory and behavioural neuropsychopharmacology services for children and young people with hypothalamic injury and disturbed sleep or behaviour (recommendation: weak; evidence: low).

12% of children are affected by sleep disturbances after surgery for craniopharyngiomas, with problems including sleep disordered breathing, sleep fragmentation, reduced sleep efficiency, sleep onset latency, and obstructive sleep apnoea, particularly in individuals with hypothalamic obesity and a history of previous radiotherapy.[126–132] Treatments such as modafinil, methylphenidate, dextroamphetamine, and melatonin have been tried with variable effects.[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 children and young people with identified neuropsychology and neurological deficits, and those who have undergone cranial radiotherapy (recommendation: strong; evidence: based on Delphi consensus).

A large quantity of literature describes various neurocognitive deficits faced by children and young people who have been treated for craniopharyngioma, 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] whereas others directly link radiotherapy to behavioural and social impairments.[144,145] Systematic comprehensive longitudinal assessment of psychological and neuropsychological function is thus necessary 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 children and young people with cystic or solid recurrences after a radiologically complete resection without previous irradiation (recommendation: strong; evidence: based on Delphi consensus).

5.2 Offer further cyst drainage before radiotherapy in children and young people with progressive, primarily cystic recurrences following initial incomplete resection without previous irradiation (recommendation: strong; evidence: based on Delphi consensus).

5.3 Offer radiotherapy with further surgery to reduce the radiation field in children and young people with progressive, primarily solid recurrences following initial incomplete resection without previous irradiation (recommendation: strong; evidence: based on Delphi consensus).

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 (recommendation: strong; evidence: based on Delphi consensus).

The management of recurrent or progressive craniopharyngiomas remains a considerable 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] 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 a very careful multidisciplinary team 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 (recommendation: weak; evidence: low).

Similar to the evidence for the use of stereotactic radiosurgery as a primary treatment, to our knowledge no high-quality paediatric evidence supports the use of stereotactic radiosurgery in recurrent or progressive craniopharyngiomas. One study consisting of a mixed cohort of adults and children showed similar 5-year progression-free survival after stereotactic radiosurgery and subtotal resection with adjuvant radiotherapy (83% *vs* 80%), and both showed better progression-free survival than subtotal resection alone (16%).[146] Some data suggest that stereotactic radiosurgery has a favourable risk profile for small tumours (<1·6 cm)^3 that are not near the optic pathway.[89,150,151]

5.6 Be aware that repeated courses of intracystic IFNα via an indwelling catheter could be considered instead of aspiration alone for recurrent cystic craniopharyngiomas (recommendation: weak; evidence: low).

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, the use of intracystic IFNα in progressive or recurrent craniopharyngiomas in children and young people should not be recommended as routine.

5.7 Be aware that systemic IFNα should only be considered in a research setting (recommendation: weak; evidence: low).

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

Conclusion

These guidelines set out evidence-based and consensus-based standards for best practice in the management of these rare paediatric tumours. The guidelines also identify a lack of high-quality evidence relating to this age group and the need for children and young people 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. Finally, these guidelines highlight the gaps in 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.

Contributors

HAS conceptualised the overarching project for the development of national guidelines for rare paediatric endocrine tumours, led the overarching scoping exercise in collaboration with the Children's Cancer and Leukaemia Group, and acquired funds for this project. H-WG and PM performed the literature searches and the initial identification of potentially relevant references. H-WG wrote the initial draft of this manuscript. All authors 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 before submission.

Declaration of interests

H-WG received a one-off consulting fee from Rhythm Pharmaceuticals for development of a drug for hypothalamic obesity (not listed in manuscript, and not licensed for this indication currently). BZ 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. HAS is the voluntary chair and founder of the SUCCESS Charity. All other authors declare no competing interests.

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