Rare endocrine tumour guidelines

Craniopharyngioma

Guideline for the management of children and young people (CYP) aged <19 years with craniopharyngioma

Children's Cancer and Leukaemia Group | the EXPERTS in CHILDHOOD CANCER

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Craniopharyngioma: Guideline for the management of children and young people (CYP) aged <19 years with craniopharyngioma

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Royal College of Paediatrics and Child Health

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Guideline for the management of children and young people (CYP) with craniopharyngioma up to the age of 19 years.

Summary of content

This guideline is intended to be a reference document for clinicians presented with the challenge of managing children and young adult patients (CYP) with craniopharyngioma up to the age of 19 years. It addresses the clinical assessment, diagnosis, treatment and follow-up of affected patients, informed by information gathered from peer reviewed scientific reports identified through a robust literature search. The expertise and experience of a range of nationally and internationally respected clinicians and scientists whose opinion has been sought as experts bring a clinically meaningful interpretation to these data, in a clear, pragmatic set of management guidelines.

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Disclosure of potential conflicts of interests

All Guideline Development Group (GDG) and Delphi consensus group participants were asked to disclose any conflicts of interests in a format adapted from NICE conflicts of interests policy. Conflicts were reviewed and all reported potential conflicts of interests are listed in Appendix 1. Funding organisations did not have any influence over the guideline development process or the recommendations provided in this guidance.

Disclaimer

Healthcare providers need to use clinical judgment, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here is the responsibility of the treating clinician and must be made in the light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

Target users of this guideline: healthcare professionals from a variety of disciplines (including paediatric endocrinology, oncology, neurosurgery, radiology, histopathology, and genetics) involved in the management and long-term follow-up of childhood and adolescent craniopharyngioma within the UK.

1. Executive summary of recommendations

Recommendation	Evidence for recommendation or consensus
Generic statements	
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 (CYP) with a suspected or confirmed craniopharyngioma.	Strong recommendation, Delphi consensus (95%)
Age-appropriate hypothalamo-pituitary multidisciplinary team (MDT) support (neurosurgery, paediatric oncology, radiation oncology, endocrinology, neuroradiology, neuropathology), including adult pituitary specialists (e.g. endocrinologists and skull base neurosurgeons) should be provided where appropriate.	Strong recommendation, low quality evidence, GDG consensus (100%)
Offer pituitary surgery performed in an age-appropriate specialist setting with on-site perioperative joint endocrine care to all CYP.	Strong recommendation, Delphi consensus (95%)
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.	Strong recommendation, Delphi consensus (83%)
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.	Strong recommendation, Delphi consensus (83%)
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.	Strong recommendation, Delphi consensus (100%)
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.	Strong recommendation, Delphi consensus (100%)
Diagnosis and investigations	
Radiology	
MRI with dedicated pituitary views in both sagittal and coronal planes (as per CCLG guidelines) should be the routine imaging modality in assessment of CYP with suspected craniopharyngioma, but where the diagnosis and/ or extent of calcification is in doubt, consider additional CT scanning.	Strong recommendation, low quality evidence, GDG consensus (100%)
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.	Weak recommendation, Delphi consensus (100%)
The pre-operative MRI report should include grading of the extent of hypothalamic involvement according to the Paris system.	Strong recommendation, high quality evidence
Vision	
Offer visual acuity, visual fields and fundoscopy before treatment in all cooperative CYP. Consider pattern visual evoked potentials in infants or disabled children but these should not be used for surveillance in the longer-term.	Strong recommendation, low quality evidence, GDG consensus (100%)
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.	Weak recommendation, Low quality evidence
Endocrinology	

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.	Strong recommendation, Delphi consensus (100%)
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.	Weak recommendation, low quality evidence
In the non-acute situation, offer combined dynamic pituitary function tests of growth hormone (GH) and cortisol reserve and, if age-appropriate, gonadotrophin secretion when feasible, before any steroid therapy when possible, as the results inform the treatment decision-making process.	Strong recommendation, Delphi consensus (100%)
Be aware that deteriorating serial thyroid function tests (low or inadequately elevated TSH concentrations with repeatedly low/ borderline low/ falling free T_4 concentrations at least 1-2 weeks apart) are sufficient for diagnosis in CYP with craniopharyngioma, without the need for a TRH test which does not adequately discriminate between hypothalamic and pituitary causes of thyroid dysfunction.	Weak recommendation, low quality of evidence
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, in the absence of a confirmed inappropriately dilute polyuria in the presence of plasma hyperosmolality (urine: plasma osmolality ratio <1.0) responsive to desmopressin, especially if the posterior pituitary bright spot is absent on MRI.	Weak recommendation, low quality of evidence
Be aware of the presence of the hypothalamic syndrome, and the possibility of performing a formal psychological assessment at diagnosis, as this may help separate disease- and future treatment-related morbidity.	Weak recommendation, low quality of evidence
Neuropsychology	
Offer all CYP with craniopharyngioma a baseline neurocognitive assessment around the time of diagnosis against which to monitor future progress.	Strong recommendation, Delphi consensus (92%)
Pathology	
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.	Strong recommendation, Delphi consensus (91%)
Be aware that Ki67 labelling or CTNNB1 mutation analysis of tissue have poor prognostic value.	Weak recommendation, low quality of evidence
Treatment	
Surgery	
Be aware that access to a surgeon with specific experience in paediatric craniopharyngioma surgery may improve overall outcomes.	Weak recommendation, low quality of evidence
Consider surgery (complete or subtotal resection or cyst aspiration) in all CYP with craniopharyngioma given the better overall and progression-free survival compared with conservative (watch and wait) management alone.	Moderate recommendation, moderate quality of evidence
Consider not proceeding with complete resection of paediatric craniopharyngiomas where there is clear evidence of hypothalamic involvement on Paris grading.	Moderate recommendation, moderate quality of evidence

Be aware of the spectrum of options available for surgical management of hydrocephalus, including but not limited to insertion of ventriculo-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.	Weak recommendation, low quality of evidence
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.	Weak recommendation, Delphi consensus (67%)
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.	Weak recommendation, low quality of evidence
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.	Weak recommendation, low quality of evidence
Be aware of the option of using high-field intraoperative MRI, although this may not improve outcomes of craniopharyngioma surgery.	Weak recommendation, low quality of evidence
Perioperative management	
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.	Strong recommendation, Delphi consensus (100%)
Be aware that perioperative hydrocortisone at stress doses could be given to CYP undergoing surgery without dexamethasone cover. If commenced consider tapering post-operatively to maintenance doses until the integrity of the hypothalamo-pituitary-adrenal axis has been established.	Weak recommendation, low quality of evidence
Be aware of the diagnoses of central diabetes insipidus (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.	Weak recommendation, low quality of evidence
Be aware of the diagnoses 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.	Weak recommendation, low quality of evidence
Radiotherapy	
Offer deferment of adjuvant radiotherapy in CYP where the surgical impression of complete resection has been confirmed on post-operative MRI and/ or CT.	Strong recommendation, low quality of evidence, GDG consensus (100%)
Consider upfront external beam radiotherapy where tumour resection is incomplete.	Moderate recommendation, moderate quality of evidence
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.	Strong recommendation, Delphi consensus (93%)
Offer radiotherapy using the gross tumour volume (GTV) defined as the dimensions of the post-operative solid and cystic tumour complex.	Strong recommendation, Delphi consensus (86%)
Offer radiotherapy using the clinical target volume (CTV) margin defined as 5 mm modified to barriers of natural spread.	Strong recommendation, Delphi consensus (100%)
Offer radiotherapy using a dose fractionation of 54 Gy (or equivalent CGE for proton beam therapy) administered in 30 fractions over 6 weeks to the planning target volume (PTV).	Strong recommendation, Delphi consensus (100%)

Consider high-energy proton beam therapy (PBT) as a radiation treatment modality for CYP with craniopharyngiomas.	Moderate recommendation, low quality of evidence, GDG consensus (100%)
Be aware that gamma knife radiosurgery should only be considered as a primary treatment for craniopharyngiomas in CYP within a research setting as there is currently insufficient evidence for its efficacy.	Weak recommendation, low quality of evidence
Other therapies	
Be aware that intracystic chemotherapies should only be considered as a primary treatment for craniopharyngiomas in CYP within a research setting as there is currently insufficient evidence for its efficacy.	Weak recommendation, low quality of evidence
Post-treatment follow-up surveillance	
Be aware that a follow-up MRI within 3-6 months of treatment may be needed assess response.	Weak recommendation, low quality of evidence
Offer MRI surveillance imaging at intervals guided by patient symptoms, definitive therapy (i.e. degree of resection and/ or radiotherapy) and by the MDT.	Strong recommendation, Delphi consensus (94%)
Offer repeat formal visual acuity and, if age-appropriate, visual field assessment within three months of definitive tumour treatment (i.e. resection +/- radiotherapy).	Strong recommendation, Delphi consensus (94%)
Offer ongoing visual follow-up at a frequency individualised according to age, residual visual function, symptoms and likelihood of tumour/ cyst regrowth.	Strong recommendation, Delphi consensus (81%)
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	Strong recommendation, Delphi consensus (100%)
Offer lifelong endocrinology follow-up for evolving hypopituitarism, with the frequency determined on an individual patient basis.	Strong recommendation, Delphi consensus (100%)
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.	Moderate recommendation, moderate quality of evidence
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.	Strong recommendation, Delphi consensus (100%)
Consider access to a designated MDT with specialist dietary, exercise, psychological and endocrine input for the management of hypothalamic obesity.	Moderate recommendation, moderate quality of evidence
Be aware of specialist sleep laboratory and behavioural neuropsychopharmacology services for CYP with hypothalamic injury and disturbed sleep and/ or behaviour.	Weak recommendation, low quality of evidence
Offer interval neuropsychological assessments until adulthood to inform clinical and educational neurorehabilitation and vocation in CYP with identified neuropsychological and neurological deficits (e.g. seizures, stroke, visual impairment) and those who have undergone cranial radiotherapy.	Strong recommendation, Delphi consensus (100%)
Management of recurrence	
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.	Strong recommendation, Delphi consensus (100%)

Offer further cyst drainage before radiotherapy in CYP with progressive, primarily cystic recurrences following initial incomplete resection without radiotherapy.	Strong recommendation, Delphi consensus (100%)
Offer radiotherapy with further surgery to reduce the radiation field in CYP with progressive, primarily solid recurrences following initial incomplete resection without radiotherapy.	Strong recommendation, Delphi consensus (100%)
Offer a repeat course of conventional radiotherapy for the treatment of disease progression or recurrence after previous radiotherapy only in exceptional cases and only after all other therapeutic modalities have been explored, given its high morbidity.	Strong recommendation, Delphi consensus (100%)
Be aware that gamma knife radiosurgery for recurrent or progressive craniopharyngiomas should only be considered in a research setting, as there is currently insufficient evidence for its efficacy.	Weak recommendation, low quality of evidence
Be aware that repeated courses of intracystic interferon-α via an indwelling catheter could be considered instead of aspiration alone in CYP with recurrent cystic craniopharyngiomas.	Weak recommendation, low quality of evidence
Be aware that systemic IFNα in CYP with recurrent craniopharyngiomas should only be considered in the context of a research trial as there is currently insufficient evidence for its efficacy.	Weak recommendation, low quality of evidence

*Based on GRADE system and Delphi consensus process (1, 2)

2. Introduction

The management of craniopharyngiomas in children and young people under 19 years of age (CYP) is challenging, not only because of their rarity, but also because of their diverse presentation to different adult and paediatric, endocrine and oncological, medical and surgical specialists. Largely benign rather than malignant, these tumours have a high survival rate. Since children with tumours have, on average, a further 68 life years ahead, their health-related quality of survival is arguably paramount. Managing CYP with craniopharyngiomas is further complicated by a lack of high quality, randomised evidence for treatment recommendations. This causes unacceptable inconsistencies and inequalities in care across units and specialties.

In order to achieve high quality care which will improve survival and reduce any secondary, long term, health-related morbidity in this young cohort, there is a need to involve age-specific and tumour-specific multidisciplinary teams (MDTs) from both CYP and adult practice in a coordinated discussion. This would also improve and expedite diagnosis - including complex endocrine and genetic screening of familial cases - acute decision making and peri-operative care as well as longer term surveillance. Oncology treatment for CYP in the UK has been centralised for decades to 16 tertiary oncological centres linked to accredited secondary paediatric oncology supportive care units (POSCUs). However, there is no age-appropriate tertiary endocrine or adult tumour-specific MDT always embedded or mandated in this service provision; the latter needs resource and development along a similar model.

Having recognised these challenges, the project board (PB) and the guideline development groups (GDGs) have, in conjunction with the Children's Cancer and Leukaemia Group (CCLG) and the British Society for Paediatric Endocrinology and Diabetes (BSPED), updated the 2005 CCLG / BSPED consensus guidelines on the management of the previous six (one pituitary and five peripheral glandular) endocrine tumours in children (3) and additionally created two new (pituitary) guidelines, this time developed according to AGREE II methodology.

2.1 Background

Craniopharyngiomas originate from embryological remnants of Rathke's pouch (4), and are rare (1.1-1.7 cases/million/year (5-7)) benign suprasellar tumours, accounting for up to 80% of tumours in this area in childhood (8, 9). They peak in incidence between 5-14 and 65-74 years of age (5, 6), but are histologically different in childhood when they are invariably adamantinomatous (rather than the adult papillary form which is vanishingly rare in childhood) (10-12). Craniopharyngiomas can also present in the neonatal period (13, 14).

Histologically they may be cystic and/ or solid, containing characteristically viscous, "engine-oil" fluid rich in cholesterol crystals (15). Although typically sporadic, human and mouse models have demonstrated that adamatinomatous craniopharyngiomas characteristically demonstrate β-catenin (*CTNNB1*) mutations resulting in hyperactivation of the Wnt signalling pathways, causing β-catenin accumulation in cell clusters over-expressing *SHH*, although increased expression of the *MAPK* pathway and various fibroblast growth factors, bone morphogenetic proteins, and cytokines have also been reported (16-20). Contrastingly, papillary craniopharyngiomas demonstrate *BRAF* V600E mutations causing hyperactivation of the *MAPK* pathway (12, 21).

As with other suprasellar tumours, symptoms may be present for prolonged durations (8 months to 8 years (22-27)) before diagnosis, most frequently relating to increased intracranial pressure or visual compromise (22, 24-26, 28-31), whilst symptoms of hypothalamo-pituitary dysfunction are often under-recognised and require direct enquiry and/ or examination (Table 1) (32, 33).

Overall 30-year survival rates are high (up to 80% (24, 34)), but this is punctuated by multiple relapses and interventions which, in turn, cause significant long-term neuroendocrine, cognitive and visual morbidity, and

premature mortality. Treatment is usually by a combined neurosurgical and/ or radiotherapeutic approach, but treatment strategies vary considerably between centres (35). Optimal management is thus unclear and the first consensus-based guidance for management of craniopharyngiomas was produced in 2005(36). We now aim to update this through a structured review of the literature and a robust Delphi consensus process using AGREE-II methodology, to provide recommendations which will improve and standardise care for such children across the country.

Table 1: Common presenting features of paediatric craniopharyngiomas ranked by median frequency.

Presenting feature	Median frequency (range)
Headaches(22, 24, 25, 28-30)	64% (51-78)
Reduction in visual acuity(22, 24-26, 28-31)	51% (23-73)
Restriction in visual fields(22, 24-26, 28-30)	46% (17-61)
Nausea/ vomiting(22, 24, 25, 28-30)	43% (31-61)
Linear growth failure/ short stature(22, 24-26, 28, 29, 32, 37, 38)	33% (14-86)
Papilloedema(29)	29%
Lethargy/ somnolence(22, 24, 32)	21% (5-22)
Cranial nerve palsy(22, 24, 29)	20% (11-27)
Weight loss(22, 24, 26, 32)	17% (5-31)
Polyuria/ polydipsia(22, 24, 26, 28, 29, 32)	16% (9-28)
Pubertal delay/ arrest(22, 24, 28, 29, 32)	10% (5-24)
Cognitive impairment(24)	10%
Blindness(24, 26)	9% (3-15)
Ataxia(4, 22, 29)	8% (7-18)
Hemiparesis(4, 22, 26, 29)	8% (7-12)
Decreased consciousness(24, 29)	8% (5-10)
Hyperphagia/ weight gain(22, 24, 26, 32)	6% (5-30)
Seizures(22, 26, 29)	5% (5-6)
Optic atrophy(24)	5%
Behaviour change/ psychiatric symptoms(22, 24, 26)	4% (3-10)
Gynaecomastia/ galactorrhoea(22)	4%
Cold intolerance(22, 24)	3% (0-5)
Precocious puberty(26, 28, 29, 32)	2% (0-3)
Sleep/ wake cycle disturbance(22)	2%

2.2 Aims and objectives

This guideline is intended to be a reference document for clinicians in several disciplines presented with the challenge of managing CYP with adamantinomatous craniopharyngioma. It covers their radiological, ophthalmological, endocrine and histopathological assessment, surgical and oncological treatment and oncological, endocrine, ophthalmological and neuropsychological follow-up, intending to provide an evidence base for future audit to optimise clinical care and reduce long-term morbidity.

The guideline addresses the following:

- Epidemiology of childhood craniopharyngioma
- Radiological +/- histological diagnosis of childhood craniopharyngioma
- Radiological staging, endocrine and visual assessment in children at diagnosis
- Neurosurgical, radiotherapeutic and chemotherapeutic treatment strategies both at diagnosis and at recurrence

- Recommendations for radiological, endocrine, visual and neurocognitive long-term follow-up
- Prognosis and survival

It is targeted at health professionals from a variety of paediatric and adult disciplines (neurosurgery, clinical (radiation) and medical oncology, endocrinology, ophthalmology, neuroradiology, neuropsychology) involved in the management and long-term follow-up of CYP with craniopharyngiomas. The inclusion of adult disciplines in this group alludes to the fact that a significant proportion of the MDT care of CYP with craniopharyngiomas in some units may include adult specialists (e.g. clinic oncology, neurosurgery), and the lifelong follow-up of these patients necessitates a clear plan for transition to adult services.

2.3 Scope & target population

This guideline covers the management of all CYP diagnosed before their 19th birthday with a confirmed adamantinomatous craniopharyngioma. It does not cover the management of patients over 19 years of age, or the management of papillary craniopharyngiomas when presenting in childhood.

2.4 Methods (see Appendix B)

Clinical questions formulated according to the defined scope of this guideline and agreed by all members of the Guideline Development Group (GDG) were written in PICO (Population, Intervention, Comparison, Outcome) format and sent out to stakeholders. Stakeholder feedback (including from the target population) was incorporated by the GDG into the finalised list of PICO questions that underpin this guideline.

Searches relating to epidemiology, diagnosis, management and follow-up of craniopharyngiomas in CYP were conducted using a combination of text words and MeSH subject headings based on the individual PICO questions constructed, via the Ovid MEDLINE (1946 – December 2014) and the Cochrane Library (including the Cochrane Database of Systematic Reviews (2016, Issue 12, Cochrane Central Register of Controlled Trials (CENTRAL, 2016 Issue 12), the Database of Abstracts of Reviews of Effect (DARE, 2015 Issue 1) electronic registries. The initial literature search was conducted in November – December 2014, and repeated in February 2017, April 2019, March 2020 and May 2021, with no significant changes to any of the recommendations (including those based on Delphi consensus) made.

The search strategy was limited by prior agreement of the overarching Project Board for all eight National Rare Paediatric Endocrine Tumour Guidelines to publications pertaining to CYP diagnosed with craniopharyngiomas before 19 years of age, including fully published case reports and case series. We excluded from our review those publications relating to craniopharyngiomas only in adults (due to the increasing incidence of papillary craniopharyngiomas in this age group), not written in the English language, and all conference proceedings, published abstracts, comments, correspondence, personal practice and book chapters.

While systematic reviews and guidelines were included as part of the review process (outside of the GRADE framework), non-systematic reviews were excluded, although these often provided additional supporting information. Titles and abstracts of studies identified from the searches were initially filtered by Hoong-Wei Gan and Paul Morillon to exclude any immediately irrelevant studies, and then subsequently fully reviewed to assess the quality of evidence by GDG members working in pairs. Any studies deemed irrelevant were excluded and the reasons for exclusion were documented.

The quality of evidence and risk of bias was assessed using the GRADE approach (1). At least two individuals independently assessed the quality of every study in each subsection of the guideline, achieving consensus for each paper included. An initial grade (high, moderate, low) based on the overall study design was increased or decreased according to study quality, consistency, directness of outcome measures, precision or reporting bias in accordance with GRADE guidelines. Overall, 271 published primary studies were reviewed in this way (241 from the initial search in 2014, 15 from February 2017, 6 from April 2019, 5 from

March 2020, and 4 from May 2021; Appendix C). The literature searches also uncovered 5 national/ international published evidence-based guidelines which are discussed and referenced within this text.

Guideline recommendations agreed by the entire GDG were made based on the highest level of evidence obtained from the GRADE process. Where evidence was lacking, or deemed too conflicting or inadequate by the GDG in order to be able to make a recommendation, the GDG then framed a recommendation, which was then taken forward to Delphi consensus. Recommendations achieving more than 70% agreement were included in the guideline, whilst the others were reframed according to feedback and subjected to a second Delphi consensus round with the same criteria (see Appendix B for full description of Delphi consensus process). Strong recommendations were made based on high and medium quality evidence, or in their absence, a Delphi consensus; whereas only weak recommendations could be made based on low quality evidence alone. In occasional situations where only low quality evidence was available, but the likelihood of obtaining stronger evidence was deemed unlikely due to the recommendation being made based on current widespread clinical best practice with no possibility of future comparison trials, the GDG did not put these forward to the Delphi consensus process but instead strengthened the recommendation based on internal consensus (recommendations 3.1.2, 3.2.1.1.a, 3.2.1.2.a and 3.2.2.3.a).

Views on the scope and the final guideline were also sought from the stakeholders and target population (craniopharyngioma patients, survivors and their families) through various patient support groups including the Childhood Cancer Parents' Alliance, Child Growth Foundation, Teenage and Young Adults with Cancer, Teenage Cancer Trust, The Brain Tumour Charity, The Pituitary Foundation and SUCCESS Charity between December 2020 and July 2021. All stakeholders were given the opportunity to comment on the final guideline recommendations made and all comments received were collated for consideration and discussion. The guideline was then externally peer reviewed by four independent reviewers (see Appendix A) and relevant changes were made before final approval by the whole GDG. The RCPCH, via the Quality Improvement Committee Clinical Lead for Evidence-Based Medicine and Appraisals provided advice on guideline development and appraised the draft for quality at different stages.

2.5 The evidence (see Appendix C)

The Delphi consensus group participants and peer review experts are listed in appendix A. The GDG identified 44 clinical questions. The number of articles excluded at each stage of the literature review process is indicated within the Tables in Appendix C. Due to the rarity of craniopharyngiomas in CYP, the majority of the identified evidence was of low or very low quality. The GDG made 32 recommendations based on identified evidence. 33 further recommendations were made based on GDG expert opinion. These were reviewed by two rounds of a Delphi consensus process. Following this, 28 recommendations achieved consensus and were included in the guideline. The words "offer" were used to indicate strong recommendations, "consider" to indicate moderate recommendations, and "be aware of" to indicate weak recommendations. Areas highlighted by the literature review and consensus process in which the GDG felt further research would be valuable, have been proposed as research recommendations (appendix E).

3. Recommendations

3.1 Generic statements

3.1.1 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 (CYP) with a suspected or confirmed craniopharyngioma. *(Strong recommendation, Delphi consensus (95%))*

3.1.2 Age-appropriate hypothalamo-pituitary multidisciplinary team (MDT) support (neurosurgery, paediatric oncology, radiation oncology, endocrinology, neuroradiology, neuropathology), including adult pituitary specialists (e.g. endocrinologists and skull base neurosurgeons) should be provided where appropriate. *(Strong recommendation, low quality of evidence, GDG consensus (100%))*

3.1.3 Offer pituitary surgery performed in an age-appropriate specialist setting with on-site perioperative joint endocrine care to all CYP. *(Strong recommendation, Delphi consensus (95%))*

3.1.4 Offer surgery by the neurosurgeon(s) nominated by the adult pituitary or paediatric neuro-oncology MDT, who can offer all possible approaches, including transsphenoidal, transcranial and endoscopic-assisted surgery. *(Strong recommendation, Delphi consensus (83%))*

3.1.5 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. *(Strong recommendation, Delphi consensus (83%))*

3.1.6 All CYP treated for craniopharyngiomas require continued lifelong care and should be transitioned to adult pituitary services, on an individualised basis, usually when growth and puberty are complete. *(Strong recommendation, Delphi consensus (100%))*

3.1.7 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 patients group. *(Strong recommendation, Delphi consensus (100%))*

To date, there is very little data on the optimum service organisation strategy for the management of craniopharyngiomas in CYP. As such, the vast majority of the above recommendations were made on the basis of the Delphi consensus process. Muller et al. (2011) observed that of 50 neurosurgical centres treating CYP with craniopharyngiomas in Germany, larger centres were less likely to undertake radical surgery and patients experienced a better quality of life than those treated in smaller centres (39). Despite lack of adjustment for confounding factors such as hypothalamic involvement and the exclusion of centre size as an independent risk factor for increased BMI in multivariate analysis in this report, the GDG and the subsequent Delphi consensus strongly supported the recommendation for specialist, age-appropriate treating centres with a decision-making interdisciplinary hypothalamo-pituitary MDT including paediatric neurosurgeons, radiation oncologists, endocrinologists, neuroradiologists, neuropathologists, and potentially also adult pituitary medical and surgical specialists. Specifically, although recommendation 3.1.2 was based on low quality evidence, the recommendation was strengthened by GDG consensus as a recognition of best practice and to harmonise this with the other Delphi consensus-based recommendations in this section.

3.2 Specific statements

3.2.1 Diagnosis & investigations

3.2.1.1 Radiology

a. **MRI with dedicated pituitary views in both sagittal and coronal planes (as per CCLG guidelines) should be the routine imaging modality in assessment of CYP with suspected craniopharyngioma, but where the diagnosis and/ or extent of calcification is in doubt, consider additional CT scanning.** ***(Strong recommendation, low quality of evidence, GDG consensus (100%))***

The combination of heterogenous solid, cystic and calcified components is characteristic of craniopharyngiomas, with the cystic components showing T_1- and T_2-weighted hyperintensity and contrast enhancement. Other differential diagnoses of space-occupying lesions in this region include low-grade/ optic pathway gliomas, germinomas, pituitary adenomas, hamartomas and Langerhans cell histiocytosis but these do not generally show this combination of features. It is well-recognised that MRI can better delineate tumour extent and facilitate pre-surgical planning than CT (10), but the latter is more sensitive for intratumoral calcification, present in 55.6-95.5% of craniopharyngiomas (10, 11, 40-42). Hence, CT in addition to MRI should be performed whenever the variability in T_1- and T_2-weighted signal intensity (10) puts the diagnosis in doubt (31, 43, 44), or the completeness of resection of a calcified tumour needs confirmation (45). There are no studies of optimal primary MRI sequences to assess craniopharyngiomas in CYP and we refer to CCLG guidelines (46) as well as parallel guidance on the investigation of Pituitary Adenomas and Thickened Pituitary Stalks in CYP for detailed recommendations on the optimal MRI sequences to image the hypothalamo-pituitary region and differentiate space-occupying lesions in this area. Given that current widespread clinical practice is to perform an MRI to diagnose a suspected suprasellar tumour, a randomised controlled trial of imaging modalities is unlikely, and the GDG therefore strengthened the above recommendation.

b. **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 preoperative assessment of craniopharyngiomas in CYP and have no clear proven role.** ***(Weak recommendation, Delphi consensus (100%)***

There is little evidence to support the routine use of advanced multimodal imaging techniques in the pre-operative assessment of CYP with suspected craniopharyngiomas. Their proximity to the skull base thwarts robust DTI and PWI image acquisition of this region, whilst arterial-spin labelled perfusion patterns can distinguish high-grade from low-grade tumours, but not histological subtype, although this data was based on a cohort only containing 4/54 patients with craniopharyngiomas (47). Two other studies assess diffusion-weighted imaging (DWI) techniques in just 5 and 6 craniopharyngioma cases respectively. The first suggested that by utilising the periodically rotated overlapping parallel lines with enhanced reconstruction (PROPELLER) DWI technique, the minimum apparent diffusion coefficient (ADC) could differentiate between craniopharyngiomas and Rathke's cleft cysts (48), whilst the second utilised a single-shot fast spin-echo DWI technique, showing that ADC readings were significantly higher in Rathke's cleft cysts than cystic craniopharyngiomas (49).

As these advanced MRI techniques become more readily available, their experimental use in assessing craniopharyngiomas may increase, but the Delphi consensus achieved after two rounds suggested that evaluation of such data must necessarily occur first before their routine use in clinical practice could be recommended. The reframed statement achieved 100% consensus in the second Delphi consensus round. As this is a negative statement the recommendation has therefore been classed as weak.

c. **The pre-operative MRI report should include grading of the extent of hypothalamic involvement according to the Paris system.** ***(Strong recommendation, high quality of evidence)***

Craniopharyngiomas are potentially highly infiltrative and invasive. Attempts to resect them from the hypothalamus are now recognised to cause severe and potentially life-threatening morbidity (26, 50-53). Overt invasion, as opposed to displacement, of the third ventricular floor –assessed on sagittal and coronal imaging – predicts adverse hypothalamic outcomes. Several studies show that hypothalamic damage increases, in a dose-dependent fashion, the risk of hypothalamic hormone deficits and obesity, and future abnormalities in glucose, insulin and ghrelin homeostasis (26, 50-52, 54). This morbidity detracts significantly from post-procedural quality of life (26, 52) and therefore pre-surgical grading of hypothalamic involvement at presentation should be recorded at MDT assessment and used to inform hypothalamus-sparing surgical treatment strategies and the pre-operative consent process.

Using the Paris grading system to differentiate patients in whom hypothalamic-sparing surgery was indicated, even at the expense of residual tumour requiring adjuvant radiation based on a retrospective cohort of 66 children with aggressively resected cranioparhygniomas, Puget et al. (2007) reduced devastating post-operative morbidity (hyperphagia, morbid obesity or behavioural dysfunction) in a prospective cohort of 22 children (26). This simple radiological classification is detailed as follows:

- Grade 0 – no hypothalamic involvement
- Grade 1 – tumour abutting or displacing the hypothalamus
- Grade 2 – hypothalamic involvement (the hypothalamus is no longer identifiable separately from the tumour)

The benefits of using this grading system have been replicated in other studies (50, 52, 55). In a study of 20 patients, Mallucci et al. (2012) selected patients for subtotal resection (STR) and radiotherapy and observed 4 progressions, 2 of whom had not received adjuvant radiation at the time and were salvaged with radiotherapy, but with no deaths, hypothalamic adipsia or hyperphagia (55). Park et al. (2013) additionally demonstrated an independent dose-response relationship between post-operative tumour grade and BMI SDS at last follow-up (50). Given the evidence, its simplicity and ease-of-use, the GDG recommended this system as a tool for assessment of hypothalamic involvement and planning surgical strategy.

3.2.1.2 Vision

a. **Offer visual acuity, visual fields and fundoscopy before treatment in all cooperative CYP. Consider pattern visual evoked potentials in infants or disabled children but these should not be used for surveillance in the longer-term.** ***(Strong recommendation, low quality of evidence, GDG consensus (100%))***

There are no studies on the sensitivity and specificity of visual function tests in craniopharyngiomas in children. The practice of assessing visual function as part of the diagnostic pathway for craniopharyngiomas is however widespread, and the GDG therefore strengthened this recommendation as best practice given that it was unlikely that a direct comparison of the three main methods of visual function testing (visual acuity, visual fields, fundoscopy) will ever be carried out due to the variation in assessment tools used based on the age and stage of development of the child.

The larger of two small studies (n=5 and n=20 respectively)(56, 57) suggested that visual acuity (VA), visual field (VF) and fundoscopy assessments detected decreased VA (52.5%), VF loss (71%), optic atrophy (60%) and papilloedema (30%) in 20 children under 14 years of age with craniopharyngiomas(57). Three other studies of children with other causes of visual impairment

concluded that quantitative preoperative assessment of VA was most important in guiding treatment decisions to preserve vision; qualitative measures were inadequate to detect even large changes in VA due to their reliance on patient cooperation and attention, often difficult in infants and those with comorbid attention deficit disorders (58-60). The presence of visual symptoms at diagnosis, particularly in CYP under 6 years of age, correlates with poorer visual outcomes (57, 61, 62).

Both optic atrophy and papilloedema are commoner in children than adults and important prognostic factors of poor visual outcome in childhood craniopharyngiomas; however the addition of colour vision or contrast sensitivity testing do not improve detection sensitivity and are not recommended. On the other hand, a relative afferent pupillary defect correlates with significant optic nerve compression and should be looked out for.

Age-dependent standardisation of VA assessment is therefore necessary to determine change over time. Teller acuity cards and grating acuity tests (e.g. the preferential looking test) are used in preverbal children, whilst computer-based recognition acuity tests (e.g. HOTV letters or Lea symbols) are used in older children who can verbalise or point. Both methods convert into reliable Snellen VA values. The logarithm of minimal angle of resolution (logMAR), where each line on an acuity chart is separated by 0.1 logMAR units is increasingly recommended to facilitate comparison of continuous VA values, and is already established in international trials of children with suprasellar and hypothalamochiasmatic gliomas.

Automated VF testing in healthy children is reliable from as young as 4 years and is feasible between 5 and 8 years of age, though testing by confrontation should be attempted as all visit (63). Older children can cooperate with Goldmann perimetry testing which better assesses the degree of field loss along both horizontal and vertical axes.

One study of craniopharyngioma patients showed abnormal VEP responses in 61.8-91.2%(64). However, because VEPs and VA reflect the central 20° and 2° of the VF respectively, severe pre-existing damage limits their ability to detect progression of visual dysfunction in the setting of paediatric optic pathway gliomas (65-67). Small changes in VEP amplitude without changes in VA require interpretation by experienced electrophysiologists who are not widely available. Thus, the use of VEPs is not recommended for long-term monitoring of craniopharyngiomas.

b. **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.** ***(Weak recommendation, low quality of evidence)***

One study of optical coherence tomography (OCT) has shown that reduced retinal nerve fibre layer thickness correlates with visual dysfunction in children with craniopharyngiomas and reduced VA(68), whilst another study of suprasellar tumours showed that this was correlated with optic tract oedema(69). OCT using the Stratus handheld OCT device has been shown to be reliable in children as young as 3 years of age (70-72). Spectral-domain OCT, which provides a much higher resolution than time-domain OCT and may therefore be more sensitive, has been safely trialled in sedated children with optic pathway gliomas as a means of testing visual function and optic nerve integrity in uncooperative infants (70). Very young infants are, however, as unlikely to cooperate with conventional OCT devices as with VA testing. It is worth noting that in adults, a thicker retinal nerve fibre layer can help predict the likelihood of recovery of vision after surgical decompression (73).

3.2.1.3 Endocrinology

a. **Offer baseline plasma endocrine biochemistry in all CYP at presentation of suspected craniopharygnioma 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. *(Strong recommendation, Delphi consensus (100%))*

b. 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. *(Weak recommendation, low quality of evidence)*

c. In the non-acute situation, offer combined dynamic pituitary function tests of growth hormone (GH) and cortisol reserve and, if age-appropriate, gonadotrophin secretion when feasible, before any steroid therapy when possible, as the results inform the treatment decision-making process. *(Strong recommendation, Delphi consensus (83%))*

Five studies (22, 31, 32, 37, 52) show that 80-90% of CYP with craniopharyngioma have hypothalamo-pituitary deficits at diagnosis if tested. Deficiencies in GH (75-81%), gonadotrophins (40-50%), TSH (25-37%), ACTH (22-25%) and AVP (7-31%) have been described. Partial AVP deficiency may be masked by concomitant ACTH deficiency and not clinically manifest as central diabetes insipidus (CDI) until glucocorticoid replacement is initiated. Mild hyperprolactinaemia, attributed to disruption of secretion of hypothalamic inhibitory dopamine is seen in 11-32%, but if severe (>2000 mU/l), should warrant exclusion of a prolactinoma (see Pituitary Adenoma guidelines). Basal plasma AFP and β-hCG concentrations should also be measured prior to any surgery to rule out a secreting germ cell tumour. However, it is worth noting that normal plasma concentrations are not 100% sensitive and measurement of cerebrospinal fluid (CSF) concentrations may require consideration if the suspicion of a germ cell tumour remains high (see Thickened Pituitary Stalk guidelines).

In order to better determine tumour- and treatment-related aetiology for endocrine deficits, the Delphi consensus fully supported both basal pituitary function and dynamic tests of GH and cortisol reserve, together with an LHRH test if age-appropriate and/ or delayed or arrested puberty is suspected, prior to treatment where possible as results can influence treatment planning for CYP with craniopharyngiomas.

It would therefore seem sensible that all patients undergo baseline pituitary function testing at diagnosis including IGF-1, TSH, free T4, LH, FSH, testosterone/ oestradiol, prolactin, 7-9 am cortisol (if patient not receiving steroid therapy) and paired early morning plasma/ urine osmolalities. In addition, AFP and β-hCG concentrations should be measured prior to any intervention to rule out a germ cell tumour. If serum concentrations are normal and the suspicion of a germ cell tumour remains high, measurement of cerebrospinal fluid (CSF) concentrations of AFP and β-hCG should also be considered (see Thickened Pituitary Stalk guidelines). Along with this, all patients should also have a full clinical assessment including documentation of auxology, height velocity and Tanner pubertal staging at diagnosis.

In order to establish the primary effect of the tumour on hypothalamo-pituitary function, prior to any therapeutic intervention, dynamic pituitary function tests of GH and cortisol (with/ without an LHRH stimulation test if delayed/ arrested puberty or hypogonadotrophic hypogonadism is clinically suspected) should be performed when feasible and clinically indicated. The results of the endocrine assessment can contribute to the treatment planning for craniopharyngiomas. GH assessment should follow GH Research Society recommendations (74), whilst the gold standard insulin tolerance test of adrenal reserve may be contraindicated in infants under 5 years and those with epilepsy or cerebrovascular disease, requiring substitution according to local guidelines.

Two studies suggest that direct stimulation with a standard dose of synacthen (SST) has a 77-91% sensitivity and 97-99% positive predictive value for excluding ACTH deficiency (75, 76). Cho et al. (2014) internally validated various plasma cortisol cut-offs in 208 normal adult controls for the insulin tolerance test (415 nmol/l), SST (480 nmol/l) and low dose synacthen test (LDST, 1 µg synacthen, 436 nmol/l) with sensitivities of 77.1% and 83.1% respectively in the latter two tests (76). Gleeson et al. (2003) found both synacthen tests had sensitivities of 91% when compered against clinical outcomes(75). The literature on the reliability of 0800 basal cortisol, other low dose synacthen tests, glucagon, metyrapone or CRH stimulation tests is otherwise of low quality (76-79). A meta-analysis of 13 observational studies by Kazlauskaite et al. (2008) suggested widely differing cut-offs for different tests with different degrees of deficiency (77). These cut-offs are also known to be assay-dependent(80), and thus the assessment of adrenal reserve requires time and endocrine expertise. In any event, a random unstimulated cortisol level before any perioperative dexamethasone or hydrocortisone cover can aid later diagnosis and should be performed.

d. **Be aware that deteriorating serial thyroid function tests (low or inadequately elevated TSH concentrations with repeatedly low/ borderline low/ falling free T_4 concentrations at least 1-2 weeks apart) are sufficient for diagnosis in CYP with craniopharyngioma without the need for a TRH test which does not adequately discriminate between hypothalamic and pituitary causes of thyroid dysfunction.** ***(Weak recommendation, low quality of evidence)***

Three studies (81-83), suggest a TRH stimulation test does not reliably discriminate between hypothalamic and pituitary thyroid disorders. Alternative methods, such as lack of the nocturnal TSH surge are not in common use (84). The European Thyroid Association and Endocrine Society have recently released guidelines on the diagnosis and management of central hypothyroidism and recommended that low or inadequately elevated TSH concentrations generated by current ultrasensitive assays, in the presence of a repeatedly low/ borderline low (on at least 2 separate determinations) or falling (>20% to previous values) free T_4 are taken as sufficient evidence of central hypothyroidism to commence replacement in those with sellar/ suprasellar disease (85, 86).

e. **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, in the absence of a confirmed inappropriately dilute polyuria in the presence of plasma hyperosmolality (urine: plasma osmolality ratio <1.0) responsive to desmopressin, especially if the posterior pituitary bright spot is absent on MRI.** ***(Weak recommendation, low quality of evidence)***

In children with polyuria and polydipsia, hyperglycaemia, hypokalaemia, hypercalcaemia, chronic renal failure and hyperthyroidism need to be excluded first. Despite the absence of formal studies on the sensitivity and specificity of water deprivation testing in this context, a recent review paper suggested that a formal water deprivation test is not required if patients with suprasellar tumours had confirmed polyuria and polydipsia and a hypo-osmolar urine paired with hyperosmolar plasma, especially if the posterior pituitary bright spot is absent (87). Two studies further correlate this latter finding with neurohypophyseal dysfunction (88, 89).

Other non-validated clues to CDI include a persistently elevated hourly urine output >2 ml/kg/hour, a low urine specific gravity of <1.005 and a urine osmolality of <300 mOsm/kg concurrent with a plasma osmolality of >300 mOsm/kg (i.e. urine: plasma ratio <1.0) (90-96). In patients with unrecognised or untreated glucocorticoid deficiency, coexisting partial CDI may not manifest as polyuria and polydipsia until glucocorticoids, permissive to renal water excretion, are commenced, whilst these same symptoms may also be masked in patients with hypothalamic hypodipsia.

Plasma and urinary AVP measurements are good markers of posterior pituitary function, but assays are not widely available and sample easily subject to processing errors (89, 97). Plasma assays for copeptin, a more stable peptide secreted stoichiometrically on AVP cleavage from its carrier protein neurophysin II are now more widely available. Several studies suggest copeptin is a more sensitive and specific surrogate marker for AVP secretion than the water deprivation test, but have largely been validated in adults so far (98-103). Only one low quality paediatric study has been conducted using a cut-off water-deprived plasma copeptin concentration of ≤3.5 pmol/l to diagnose complete/ partial central DI, with suboptimal sensitivity (75%) and specificity (83%) (104). Therefore, the GDG could not recommend its routine use in CYP, although it may add information in cases where there is hypodipsia.

A trial of desmopressin treatment should reduce fluid intake, thirst, plasma sodium and osmolality, but if there is persistent hypernatraemia, a formal biochemical diagnosis of central DI may need to be sought with a water deprivation test.

f. **Be aware of the presence of the hypothalamic syndrome, and the possibility of performing a formal psychological assessment at diagnosis, as this may help separate disease- and future treatment-related morbidity.** ***(Weak recommendation, low quality of evidence)***

Tumour and/ or treatment-related hypothalamic injury can cause devastating social and neuroendocrine sequelae which severely impair quality of life, and manifest predominantly as morbid inexorable obesity, neuropsychiatric disturbance, temperature dysregulation and thirst impairment. Formal questionnaires such as the Epworth Sleepiness Scale (105), Pittsburgh Sleep Quality Index (106), and the Dykens Hyperphagia Questionnaire Score (107) have not been evaluated in CYP with craniopharyngiomas, but given the high incidence of such hypothalamic features in this cohort (108-113), the GDG suggest that some form of assessment of hypothalamic dysfunction is considered in baseline pre-surgical assessments of hypothalamic dysfunction to inform treatment planning as part of hypothalamic-sparing strategies.

3.2.1.4 Neuropsychology

a. **Offer all CYP with craniopharyngioma a baseline neurocognitive assessment around the time of diagnosis against which to monitor future progress.** ***(Strong recommendation, Delphi consensus (92%))***

Despite a vast body of literature documenting post-treatment long-term neurocognitive deficits in survivors of childhood craniopharyngioma (see Section 3.2.2.5.k), there is no similar data at presentation in CYP. However, this is now being collected, at least before radiation if not before surgery as part of an international trial of proton beam irradiation, and was also strongly supported as a recommendation by the Delphi consensus panel of experts and achieved 92% agreement.

3.2.1.5 Pathology

a. **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.** ***(Strong recommendation, Delphi consensus (91%))***

In the absence of any evidence, the GDG agreed histopathological confirmation of the diagnosis of craniopharyngioma in CYP was important before instituting any definitive treatment, and framed a recommendation to this effect. However, although several Delphi panel experts agreed with histological confirmation, especially before any radiotherapy was imposed, this did not reach 70% agreement as there remained concerns that urgent definitive surgery should not be delayed when appearances at surgery were often typical (e.g. cystic "engine oil" fluid). The GDG subsequently considered that some cystic cases may proceed to radiotherapy after aspiration

alone without definitive histology but still felt it good practice to obtain either tissue confirmation or characteristic fluid crystals in all but the most exceptional cases. The reframed recommendation above achieved 80% agreement in the second Delphi consensus.

b. **Be aware that Ki67 labelling or *CTNNB1* mutation analysis of tissue have poor prognostic value.** ***(Weak recommendation, low quality of evidence)***

Molecular research in craniopharyngiomas in both mice and humans is currently a very active field. Potential new biomarkers, and new paracrine and inflammatory pathways are rapidly being discovered and explored with new therapeutic targets being identified (114). Retrospective cohort studies of a wide range of molecular markers (β-catenin, E-cadherin, vimentin, GH receptor, SMO, SUFU, CXCL12, CXCR4) have been correlated with overall survival (OS) or progression-free survival (PFS) (115-119), but the data is conflicting and not all studies include all markers. Based on the evidence to date, the GDG did not feel that Ki67 labelling or *CTNNB1* gene sequencing, the most commonly used markers, could be used to reliably predict outcome. There may, however be diagnostic value in assessing *CTNNB1* status and other molecular markers in some cases to aid with diagnosis.

3.2.2 Treatment

3.2.2.1 Surgery

a. **Be aware that access to a surgeon with specific experience in paediatric craniopharyngioma surgery may improve overall outcomes.** ***(Weak recommendation, low quality of evidence)***

In all five primary publications assessing the effect of individual or unit neurosurgical experience on outcomes, evidence was of low quality, patient numbers were small, neurosurgical techniques and outcomes compared were variable, with very little data on long-term quality of survival (120-124). One survey of the members of the American Society of Paediatric Neurosurgeons, documenting outcomes in 139 children with craniopharyngioma reported a significant difference in the outcome of radical surgery according to surgeon experience (122). Another evaluated only the endoscopic endonasal transsphenoidal approach without any long-term quality of outcomes in a population of mainly adult patients that both ENT surgeons and neurosurgeons were equivalent operators in this area(124).

The recommended surgical approach was not formally evaluated as a PICO question but the evidence from a meta-analysis suggests that surgeons tailor their approach according to neuroanatomical correlates, technique availability and surgical experience. Outcomes between transcranial and transsphenoidal approaches in CYP with craniopharyngiomas (n=2955 vs. 373 respectively), show similar overall survival but higher neurological morbidity, central DI, and visual deterioration in the transcranial group, although these patients also had more hydrocephalus, larger tumours and a greater incidence of hypothalamic involvement (125). Thus, it would seem prudent to suggest that units managing CYP with craniopharyngiomas should have specialist experience and be able to offer all the possible neurosurgical approaches.

b. **Consider surgery (complete or subtotal resection or cyst aspiration) in all CYP with craniopharyngioma given the better overall and progression-free survival compared with conservative (watch and wait) management alone.** ***(Moderate recommendation, moderate quality of evidence)***

c. **Consider not proceeding with complete resection of paediatric craniopharyngiomas where there is clear evidence of hypothalamic involvement on Paris grading.** ***(Moderate recommendation, moderate quality of evidence)***

We found no randomised-controlled trials or observational studies comparing outcomes after

surgical intervention against a watch and wait strategy. One study utilising disaggregated national registry data from the Surveillance, Epidemiology and End Results (SEER) Programme of the USA National Cancer Institute showed OS was improved after subtotal resection (STR, HR 0.45 (95% CI 0.23-0.85)), but not gross total resection (GTR, HR 1.22 (95% CI 0.71-2.08)) compared with observation or biopsy (7).

By contrast, there are several, largely retrospective cohort studies and systematic reviews comparing outcomes of GTR with STR with or without subsequent adjuvant radiotherapy (7, 34, 126-140). These, however, variably stratify or include either tumour location or hypothalamic involvement in their analyses. The reported relative efficacy of GTR vs. STR in improving long-term survival is inconsistent across these studies though most suggest better PFS or OS after GTR compared with STR (126, 130-132, 134-137, 140). However, where a grading system of hypothalamic involvement has been incorporated into multivariate analyses, GTR has not been associated with improved outcomes (34) or indeed, in some cases, has worsened PFS compared to STR with adjuvant radiotherapy (139).

There are several systematic reviews of surgical treatment for paediatric craniopharyngiomas. The latest reported resection recurrence and long-term follow-up in 377 children from 109 studies and found no difference in 1- and 5-year PFS between GTR (89% and 77% respectively) and STR with adjuvant radiotherapy (77% and 73% respectively)(126). However omitting adjuvant radiation after STR significantly reduced both 1-year (76% vs. 84%) and 5-year (43% vs. 73%) PFS. 22 patients who were only biopsied and given intracystic treatment had similar PFS to those undergoing STR and radiotherapy, but the analysis did not control for selection bias and these cases are likely to have been smaller purely cystic tumours not directly comparable to larger solid types.

The importance of adjuvant radiotherapy in stabilising any residual disease has been repeatedly reported. A large literature review of 43 studies in 1716 patients undergoing radiotherapy for craniopharyngoma between 1990 and 2012 reported 10-year local control rates of between 77-100% whilst the long-term morbidity and incidence of new life-threatening CDI was higher after radical surgery than after limited surgery with adjuvant radiotherapy (127, 141). Other studies also support the hypothesis that adjuvant radiotherapy, in combination with STR, achieves equivalent PFS and OS to GTR and is superior to STR alone (see section 3.2.2.3) (130, 137).

Only one observational prospective multicentre study of children surgically treated for craniopharyngioma (KRANIOPHARYNGEOM 2000) across 46 centres of varying pituitary surgical expertise reported better 3-year event-free survival (defined as death, progression or relapse) after GTR compared with STR (134). Hypothalamic involvement however has recently been shown to negatively impact on OS, but was not considered as a variable in the analysis for KRANIOPHARYNGEOM 2000 (34).

Higher morbidity and late mortality results from panhypopituitarism, particularly post-treatment CDI and hypoglycaemia secondary to ACTH deficiency (32, 141-145). One population-based study of adults and CYP reported respective standardised mortality ratios (SMR) for hypopituitarism and CDI of 4.3 (95% CI 3.1-5.8) and 6.1 (95% CI 3.5-9.7) times that expected respectively (143). CDI together with either hypothalamic adipsia, and/ or ACTH deficiency, is a particularly significant risk factor for mortality (32). A recent aggregated data analysis from three UK centres treating CYP with craniopharyngiomas over 40 years showed that over successive treatment eras, along with more conservative surgical treatment strategies involving a reduction in attempted GTR, the rates of CDI, gonadotrophin deficiency, and panhypopituitarism were lower, with no change in the rates of hypothalamic syndrome or obesity (146). Avoidance of further hypothalamic damage during surgery is therefore recommended.

In summary, moderate quality evidence indicates better survival after GTR compared with STR, with low quality evidence suggesting that adjuvant radiotherapy to the residual can ameliorate

the latter. Radiological evidence of hypothalamic damage predicts higher mortality. Given the indirect, moderate quality evidence that CDI and ACTH deficiency are associated with late mortality in CYP with craniopharyngioma, the GDG considered that hypothalamic Paris grading of craniopharyngiomas was important in determining the resectability of the tumour (i.e. GTR vs. STR) and the overall surgical treatment strategy to avoid further hypothalamic harm (see section 3.2.1.1.c).

d. Be aware of the spectrum of options available for surgical management of hydrocephalus, including but not limited to insertion of an ventriculo-peritoneal shunts, external ventricular drain, transventricular endoscopic cyst drainage, transsphenoidal endoscopic cyst drainage or insertion of an Ommaya reservoir into a craniopharyngioma cyst, tailoring these to each patient. *(Weak recommendation, low quality of evidence)*

e. 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. *(Weak recommendation, Delphi consensus (67%))*

f. 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. *(Weak recommendation, low quality of evidence)*

g. 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. *(Weak recommendation, low quality of evidence)*

There are no direct comparative prospective or retrospective efficacy studies of surgical treatment of hydrocephalus in craniopharyngioma. Five publications, with small numbers of children with craniopharyngioma (147-151), describe management of hydrocephalus but do not record the prevalence of each technique. The various techniques used have included insertion of an Ommaya reservoir (147, 151), ventriculo-peritoneal shunting (148), transventricular endoscopic periventricular cyst drainage (149), and endoscopic fenestration (150). Two-thirds of the Delphi consensus panel agreed that in the presence of a predominantly cystic craniopharyngioma and hydrocephalus, the cyst should first be decompressed before reviewing the need to treat the hydrocephalus itself.

Of eleven publications reviewed to assess the effectiveness of cyst decompression in the context of additional therapy (150, 152-161), the majority were case series and only one retrospective cohort study in 52 patients concluded that insertion of an Ommaya reservoir reduced the rate of relapse (153). Only 27% of patients subsequently experienced cyst reaccumulation, four being retreated with intracystic bleomycin. Other publications described various stepwise approaches (either Ommaya reservoir insertion or endoscopic cystic drainage) to draining large cystic craniopharyngiomas either in cystic recurrences or to allow for more definitive tumour resection using microsurgical techniques (150, 152, 154, 155, 157). Given these differing unproven approaches the GDG considered a stepwise surgical approach to management of large cystic craniopharyngiomas is suggested.

h. Be aware of the option of using high-field intraoperative MRI, although this may not improve outcomes of craniopharyngioma surgery. *(Weak recommendation, low quality of evidence)*

Six publications referred to high field intra-operative MRI in craniopharyngiomas but none included a comparator group and the evidence of benefit was weak (160, 162-166). Hofmann et al. (2011) found it helped determine the extent of tumour resection in 25 tumours judged difficult from pre-operative imaging (162), whilst Nimsky et al. (2004) acknowledge it may change surgical strategy in 200 adult and paediatric patients mostly undergoing craniotomy or transsphenoidal

surgery for intracranial tumours (164). These were mostly gliomas or pituitary adenomas, but their earlier study in craniopharyngiomas concluded similarly though unpredictable recurrences still occurred (163). Intraoperative MRI has also been reported to aid accurate placement of cyst catheters (160, 163).

3.2.2.2 Perioperative management

a. **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.** ***(Strong recommendation, Delphi consensus (100%))***

Perioperative dexamethasone to reduce peritumoral oedema has been widely used despite the absence of much evidence from randomised controlled trials since its discovery in 1961, that high-dose corticosteroids dramatically alleviated the mortality and morbidity of brain tumour surgery (167). One randomised trial showed that a dose of 4 mg daily is sufficient to ameliorate long-term morbidity in adults (168). Roth et al. (2010) reviewed steroid use in neuro-oncology and concluded that they are likely overused in this context, but could find no evidence from which to produce definitive guidance (169). There are likewise no studies specific to CYP with craniopharyngiomas. A recent study of adult brain tumour patients showed that a more rapid taper of dexamethasone led to a reduction in the incidence of hypertension, with no change in neurological morbidity; however, the doses and duration of dexamethasone used in this study were not comparable to paediatric practice (170). Another randomised controlled trial of adult pituitary adenoma patients undergoing transsphenoidal surgery showed that perioperative hydrocortisone and dexamethasone resulted in a higher incidence of post-operative headaches and patients being discharged on long-term glucocorticoids for adrenal suppression, although this latter difference was not significant (171).

Given the suppressive effects of corticosteroids on growth, bone health and adrenal function, the GDG put forward two statements to clarify the use of dexamethasone to the Delphi consensus panel. These statements were modified in accordance with comments received in Round 1 and achieved 87% agreement in Round 2.

b. **Be aware that perioperative hydrocortisone at stress doses could be given to CYP undergoing surgery without dexamethasone cover. If commenced this consider tapering post-operatively to maintenance doses until the integrity of the hypothalamo-pituitary-adrenal axis has been established.** ***(Weak recommendation, low quality of evidence)***

We found one study of adults with tumours other than craniopharyngiomas undergoing pituitary surgery with intravenous hydrocortisone cover followed by early re-assessment of hypothalamo-pituitary-adrenal status by morning serum cortisol concentrations and insulin tolerance testing (172). Just one patient with normal pre-operative adrenal status required hydrocortisone replacement long-term and none had adrenal crises but there was no control group. A meta-analysis of routine perioperative hydrocortisone cover in adults with pituitary adenoma found insufficient data to make a recommendation but reported an early postoperative low prevalence of adrenal insufficiency (0.96-12.9%) (173). Previous guidelines in adults with pituitary tumours recommended emergency peri-operative hydrocortisone cover for at least 48 hours in cases where selective adenomectomy is not possible (see section 3.2.2.5.d & g) (174). Since selective resection of the pituitary is unlikely in craniopharyngioma, the GDG suggests that CYP not receiving dexamethasone for neuroprotection, but undergoing surgery should routinely receive "stress doses" of hydrocortisone pre-operatively to prevent acute adrenal insufficiency, continued until the hypothalamo-pituitary-adrenal axis has been fully evaluated and proven intact. Patients with intact pre-operative adrenal function and small pituitary masses undergoing minor non-resective surgery, could discontinue hydrocortisone 24-48 hours post-operatively with monitoring of adrenal status by morning serum cortisol concentrations, though there is no consensus on the cut-off level for hydrocortisone supplementation (174).

There is also no consensus on the most appropriate perioperative hydrocortisone schedule, the commonest regimens commenced at induction of anaesthesia being:

- 1 or 2 mg/kg (max 100 mg) intravenously 6-8 hourly
- 1mg/kg (max 100 mg) as a loading dose and then as a continuous infusion over 24 hours
- 25 mg in children <1 year, 50 mg in children between 1 and 5 years and 100 mg for those >5 years intravenously 6-8 hourly
- Triple normal oral replacement daily dose given as a daily continuous intravenous infusion or in 4 divided doses intravenously.

After 24-48 hours, or when the patient is tolerating oral intake, the intravenous route can be changed to oral and hydrocortisone doses reduced to double maintenance in three or four equally divided doses. Provided the patient remains well, this can then be weaned after a further 24 hours to replacement doses (estimated at 8-10 mg/m^2 daily) in three divided doses given in a circadian rhythm, until confirmation of adrenal integrity.

c. **Be aware of the diagnoses of central diabetes insipidus (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.** ***(Weak recommendation, low quality of evidence)***

The diagnostic criteria for salt and water imbalance disorders, reviewed by several authors (175, 176) and discussed in section 3.2.1.3.e, include both clinical and biochemical findings. After excluding other causes of diuresis of intravenous fluids administered perioperatively, hyperglycaemia and diuretic administration, the diagnosis of CDI should be suspected in the presence of hypotonic (<300 mOsm/kg) polyuria (>2 ml/kg/hour) in conjunction with hyperosmolar plasma (>300 mOsm/kg). Patients with CDI, intact thirst and free access to oral fluids may not develop hypernatraemia and hyperosmolality. In practice, a urine output of >4-5 mls/kg/hour for at least 2 consecutive hours, paired with a urine/plasma osmolality ratio <1, or hourly urinary specific gravity ≤1.010, in the immediate postoperative period, is highly indicative of central DI.

Where thirst is intact, patients with CDI should be allowed free access to oral fluids. If they are unable to drink or if there is evidence of adipsia, IV fluid replacement in the form of 0.45% sodium chloride in eunatraemic patients or 0.9% sodium chloride for extrarenal losses or hypernatraemic patients can be instituted. Fluid losses in excess of maintenance plus insensible losses (300 ml/m^2/day) should be replaced by matching fluid balance (and associated electrolyte concentrations) 6- to 8-hourly, whilst remaining alert to acute triphasic response changes. Desmopressin can reduce total daily fluid requirements but doses require titrating according to urine output and pre-dose plasma/ serum sodium concentrations. Caution should be exercised until/ unless CDI is stable and permanent(87). Hyponatraemic may result from desmopressin overdose and doses should be withheld until sodium concentrations normalise to avoid cerebral oedema.

CYP undergoing craniopharyngioma surgery can experience the triphasic response, consisting of an initial phase of CDI within the first 24-48 hours postoperatively, followed by SIADH about a week after, finally resulting in permanent CDI 1-2 weeks later (176). Variations of this pattern occur more often than in adults and therefore all CYP require careful monitoring (177). Cerebral salt-wasting syndrome (see Section 3.2.2.2.m) can also occur concurrently during any of the three phases (175, 178). Although two newer very low quality studies suggest that postoperative plasma copeptin may be useful in diagnosing CDI, both of these studies were carried out in adults, who are less likely to demonstrate the triphasic response (177, 179, 180). Additionally, in UK practice, obtaining plasma copeptin measurements may not be sufficiently rapid to aid with decision-making in these patients.

d. **Be aware of the diagnoses 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.** ***(Weak recommendation, low quality of evidence)***

Data from two studies (181, 182) suggest SIADH is clinically characterised by a significantly reduced urine output of inappropriately high urine osmolality (>500 mOsm/kg) in the presence of euvolaemia/hypervolaemia, a low plasma sodium (<132 mmol/l) and osmolality (<270 mOsm/kg), with patients often reporting increased thirst. Urine sodium loss is usually >20 mmol/L (but fractional excretion of sodium <1), with suppressed plasma renin activity, low haematocrit, low plasma urea, and uric acid(175, 178). The therapeutic intervention for SIADH is fluid restriction. In severe cases, only insensible losses (300 ml/m^2/day) may need replacement. The use of vasopressin receptor antagonists (e.g. tolvaptan) is limited in CYP and currently requires more research before it can be routinely recommended (183, 184). Normal adrenal and thyroid status should be confirmed and contributory renal or iatrogenic pathologies (e.g. diuretics, anti-epileptic medications) should be excluded prior to confirming the diagnosis of SIADH (87).

If hyponatraemia is coupled with hypovolaemia and a concentrated polyuria, the diagnosis of transient cerebral salt-wasting should be considered. The diagnostic criteria for cerebral salt-wasting syndrome in CYP is limited to case series and case reports after interhemispheric operative approaches or subarachnoid haemorrhage (185-188). Usually, it is characterised by a net negative water and sodium balance, hypotension and/ or tachycardia, but severe dehydration will reduce the polyuria which can be unmasked by a saline challenge. Biochemically, there is a low plasma osmolality, high urine osmolality with significant natriuresis (urinary sodium >40 mmol/l, fractional excretion of sodium >1) with urinary sodium excretion substantially higher than sodium intake, normal/ high haematocrit and serum urea. Plasma renin activity may be high-normal or frankly elevated; occasionally it is depressed or normal. The pathophysiology may be driven by brain natriuretic peptide (BNP) or atrial natriuretic peptide (ANP) (186, 187), but assays are neither widely available nor is their predictive value known. Treatment is by water and salt replacement and mineralocorticoid administration (fludrocortisone) has occasionally been used for treatment at doses of 0.025–1 mg/day (185, 186), but can cause hypokalaemia (in 73% of patients) and hypertension. Rarely, aggressive fluid replacement is required with central venous pressure monitoring. Recovery is usually within 24-72 hours, heralded by a rise in plasma sodium, whilst prolonged courses should raise suspicion of infection or other pathology (87).

In both cases, the detailed management of hyponatraemia is beyond the scope of this guideline and clinicians should refer to international expert recommendations (189). This includes recommendations regarding the use of hypertonic saline in the scenario of symptomatic hyponatraemia (e.g. seizures).

3.2.2.3 Radiotherapy

a. **Offer deferment of adjuvant radiotherapy in CYP where the surgical impression of complete resection has been confirmed on post-operative MRI and/ or CT.** ***(Strong recommendation, low quality of evidence, GDG consensus (100%))***

b. **Consider upfront external beam radiotherapy where tumour resection is incomplete.** ***(Weak recommendation, low quality of evidence)***

c. **Offer deferment of radiation until tumour progression is evident on a case-by-case basis where the MDT considers morbidity of radiation may outweigh its benefits in very young**

children or those with minimal residual disease. *(Strong recommendation, Delphi consensus (93%))*

GTR of craniopharyngiomas is achievable with acceptable morbidity in only a minority of selected cases, but if radiologically confirmed, gives excellent and comparable control rates to STR and adjuvant radiotherapy. 3 retrospective cohort studies additionally show no additional benefit of adjuvant radiotherapy in the context of a GTR, although this does not confer additional long-term morbidity(24, 137, 190). However given the widespread practice of not administering radiotherapy after GTR, higher quality studies examining outcomes in this context are highly unlikely, and therefore the GDG consensus was to strengthen this recommendation.

Two systematic reviews of 5-year PFS show comparable rates after GTR or STR with radiotherapy (77 vs. 73%, n=377(126); 67% vs. 69%, n=442 (136)). In another cohort of 122 patients aged 11 to 52 years, 24% patients undergoing GTR alone had similar OS and PFS to those undergoing STR and radiotherapy (130). However, STR without adjuvant radiotherapy results in unacceptably poor local control rates (126, 130, 136) and may increase the risk of long-term visual deterioration (24).

Hence in cases where GTR poses unacceptable hypothalamic morbidity, STR with adjuvant radiotherapy (within 3 months) is recommended, but the optimal timing of the latter may be delayed until disease progression (salvage radiotherapy) in very young children or those with minimal residual disease where the MDT feels the balance of harm of radiation (e.g. neurocognitive decline, neurovascular events) outweighs its benefit. Two studies suggest no difference in survival rates with this salvage strategy but report a concerning increased rate of visual and endocrine morbidities and of CDI (191, 192). The GDG considered that whilst a watch and wait policy may therefore be appropriate in some very young patients after STR alone, this must be accompanied by close imaging and ophthalmological follow-up to address the high recurrence risk. This recommendation was supported by 86% of the Delphi consensus panel.

d. Offer radiotherapy using the gross tumour volume (GTV) defined as the dimensions of the post-operative solid and cystic tumour complex. *(Strong recommendation, Delphi consensus (86%))*

e. Offer radiotherapy using the clinical target volume (CTV) margin for radiotherapy defined as 5 mm modified to barriers of natural spread. *(Strong recommendation, low quality evidence, Delphi consensus (100%))*

GTV should include all post-operative solid and cystic components in the tumour bed, but whist the pre-operative volume requires consideration it should be adjusted to reduce the volume of normal brain irradiated (193, 194). Merchant et al.'s study of 88 children of median age 8.5 years receiving conformal or intensity modulated radiotherapy between 1998 and 2009 showed no difference in 5-year PFS when the 10 mm CTV was reduced to 5 mm in 2003 (88.1% vs. 96.2% respectively)(193). In the absence of further studies the above statements were put to the Delphi consensus panel and received 86% and 100% approval respectively.

f. Offer radiotherapy using a dose fractionation is 54 Gy (or equivalent CGE for proton beam therapy) administered in 30 fractions over 6 weeks to the planning target volume (PTV). *(Strong recommendation, low quality evidence, Delphi consensus (100%))*

Reported focal radiation doses for craniopharyngiomas in CYP are 50-54 Gy in 28 – 30 daily fractions over 6 weeks (193, 195-197). There are no randomised data comparing dose regimens but a study of 19 children showed higher rates of recurrence when doses of less than 54 Gy were used compared with 54 Gy or more (50% vs. 15%)(198). To refine the optimum dose fractionation regimen in the absence of clear evidence the GDG put forward two statements to the Delphi consensus process, differing only in the total dose (50 Gy vs. 54 Gy) delivered over the same

number of fractions (30) and duration (6 weeks). 100% of the radiation panel of experts agreed with the use of a total dose of 54 Gy, rather than 50 Gy.

g. **Consider high-energy proton beam therapy (PBT) as a radiation treatment modality for CYP with craniopharyngiomas.** ***(Moderate recommendation, low quality of evidence, GDG consensus (100%))***

Despite the absence of clear evidence of benefit in children receiving radiation from protons compared to conventional or intensity-modulated photons in either OS, PFS, reduction in late neurocognitive toxicity or second tumour rates, proton radiation has increasingly become the standard of care for CYP with craniopharyngioma in the UK since 2010, with long-term clinical outcome data awaited (199-201). Only three studies compared photons with PBT, finding no difference in local control rates or OS. Leroy et al's (2016) systematic review of PBT in 15 different paediatric cancers concluded that there was insufficient evidence to support or refute its use in craniopharyngiomas (202), whilst Bishop et al's (2014) retrospective two-centre comparison found no difference in OS or PFS in 31 intensity-modulated radiotherapy- vs. 21 PBT-treated patients (192). However, median follow-up times were significantly shorter in the PBT group (33 months vs. 106 months, $p<0.001$) and data on the long-term toxicity of protons was lacking. Merchant et al. (2008) reported cognitive outcomes after PBT compared to conformal photon irradiation in four childhood brain tumour types, including 10 with craniopharyngioma, and found that PBT resulted in better dose distribution and significantly higher IQ scores (203), but this data requires confirmation in further studies. For these reasons the GDG felt it reasonable to suggest considering high energy PBT where available pending the outcomes of ongoing research, thereby strengthening the recommendation.

It is also worth noting that with increasing experience there is some concern that radiation necrosis in the brainstem may be more frequent in children treated with proton therapy (204, 205). This is currently unconfirmed and not well understood but some PBT centres are taking a precautionary approach to brainstem doses where appropriate. Thus, in the absence of good quality evidence demonstrating higher doses conferring improved local control rates, for a benign tumour such as craniopharyngioma, a dose of 50.4 CGE in 28 fractions may be favoured but this is neither consensus- nor evidence-based. It is therefore important that those centres employing this approach collect and report their outcomes.

h. **Be aware that gamma knife radiosurgery should only be considered as a primary treatment for craniopharyngiomas in CYP within a research setting as there is currently insufficient evidence for its efficacy.** ***(Weak recommendation, low quality of evidence)***

Stereotactic (gamma knife) radiosurgery (SRS) usually delivers a single large radiation dose of 12-14 Gy to a small volume with high precision. Excellent local control with low toxicity has been reported in appropriately selected adults with craniopharygioma, including recurrent tumours (206), but there is little long-term outcome data in children in whom the neurocognitive late toxicity may be greater and whose craniopharyngiomas are often too large for SRS. No SRS studies with children incorporate a comparison group (206-214), and therefore, SRS tends to be reserved for specific individual indications such as small volume recurrence (see section 3.2.2.6.e) (215). Stereotactic techniques can also deliver conventionally fractionated radiotherapy with comparable results to conformal external beam radiotherapy (194, 197). Further research is needed to determine whether SRS has a better risk-benefit profile than fractionated radiation and a role in primary treatment of craniopharyngiomas in CYP.

3.2.2.4 Other therapies

a. **Be aware that intracystic chemotherapies should only be considered as a primary treatment for craniopharyngiomas in CYP within a research setting as there is currently insufficient evidence for its efficacy.** ***(Weak recommendation, low quality of evidence)***

The absence of high volume studies of intracystic chemotherapies and/ or comparisons with sham cyst aspirations or saline controls means the evidence for its efficacy as a primary treatment for craniopharyngiomas over cyst aspiration alone is lacking, with remaining concerns of neurotoxicity. However, interferon-α (IFNα) has increasingly become the preferred option for monocystic disease in light of the lower risk of neurotoxicity from leakage compared to bleomycin or radioisotopes, but further prospective randomised trials to establish risk-benefits are required before approval as first-line therapies (216).

i. Intracystic interferon-α (IFNα)

Cavalheiro et al's (2010) prospective multicentre single-arm study of 60 patients with predominantly cystic craniopharyngomas, in whom 39 received IFNα as a primary treatment, reported control rates of 78.3%, but 13 patients required further surgical excision over a follow-up period of up to 4 years (217). No mortality was reported but treatment was continued with largely minor side effects (30%; e.g. headache, eyelid oedema, fever, chronic fatigue syndrome and arthritis) and worsening endocrinopathy (13%). Kilday et al's (2017) retrospective multicentre analysis of 56 CYP with craniopharyngiomas suggested that IFNα delayed progression slightly compared to previous therapy, particularly in those with predominantly cystic craniopharyngiomas (1.3 years vs. 0.3 years, $p<0.001$), but the number of doses administered were inconsistent between centres (218). There are also recent reports of neurotoxicity and therefore a positive leak test is now a relative contraindication to intracystic IFN-α treatment (219). Further sham crossover controlled studies are being developed internationally.

ii. Intracystic bleomycin

Published literature on intracystic bleomycin is limited to meta-analyses of low quality studies which consistently conclude its use in children should only be in the context of a trial with close clinical and radiological monitoring (220-223). Only three single-centre, single-arm studies reported on a small subcohort where the majority received conventional therapies (224-226).

iii. Intracavitary irradiation

The evidence for using of intracavitary radionuclides (e.g. ^{32}P, ^{90}Y, ^{186}Re) is limited to low volume single-centre, single arm studies or case series, usually after multiple recurrences, without comparison to more conventional treatments (227-235). As with other intracystic therapies, there is a lack of data from which to determine their efficacy and risk-benefit profile.

iv. Systemic IFN-α

Systemic IFN-α has never been used as a primary therapy in craniopharyngiomas and there are only two single-arm studies of its use in recurrent tumours (236, 237). The GDG therefore could neither support nor refute its use (see Section 3.2.2.6.g).

3.2.2.5 Post-treatment follow-up surveillance

a. **Be aware that a follow-up MRI within 3-6 months of treatment may be needed to assess response.** ***(Weak recommendation, low quality of evidence)***

b. **Offer MRI surveillance imaging at intervals guided by patient symptoms, definitive therapy (i.e. degree of resection and/ or radiotherapy), and by the MDT.** ***(Strong recommendation, Delphi consensus (94%))***

Only two small retrospective cohort studies with no set protocols for the frequency of serial imaging have examined radiological tumour size after radiotherapy (238, 239). Of these, one study showed continued expansion up to 15 months, and shrinkage up to 68 months after radiotherapy (238), while the other showed tumour volume increased up to 224% in 52% of 21 CYP with craniopharyngiomas up to 5 months after radiotherapy with a median time to maximal tumour shrinkage of 9.5 months (range 3.5-39.9 months) (239). These studies provide a range for

post-radiation tumour response and confirms the clinical impression that tumour enlargement, particularly cyst reaccumulation may be triggered by radiation therapy before shrinkage and may not always require intervention. The GDG could not hence explicitly recommend an optimum imaging interval and 94% of the Delphi consensus panel agreed with this decision. However, there may be a need for an immediate post-operative MRI +/- CT within 48-72 hours, and because images may be difficult to interpret, particularly if the sellar floor has fat-packing material, supplementary fat-saturated post-contrast imaging is advocated. Early 3 month imaging and 3-6 monthly follow-up after surgery and/ or irradiation is commonly performed and follows neuro-oncology PBT trial protocols.

c. **Offer repeat formal visual acuity and, if age-appropriate, visual field assessment within three months of definitive tumour treatment (i.e. resection +/- radiotherapy).** ***(Strong recommendation, Delphi consensus (94%))***

d. **Offer ongoing visual follow-up at a frequency individualised according to age, residual visual function, symptoms and likelihood of tumour/ cyst regrowth.** ***(Strong recommendation, Delphi consensus (81%))***

Recovery of visual deficits is not usual after the first post-operative month (240, 241), and children under 6 years with visual deficits at diagnosis of craniopharyngioma are at high risk of poor visual outcomes (61, 62). There is no evidence for an optimal visual surveillance protocol and the sensitivity and specificity of VA and VF testing for detecting radiological recurrence, which it cannot replace, is unknown (see section 3.2.2.5). Nevertheless, tumours must be sizeable before new visual deterioration is documented, delaying therapy and reducing the likelihood of reversing visual impairment. Visual assessments are important to determine visual impairment in developing CYP who should be referred to the appropriate service for the visually impaired and for special educational support. These statements achieved 94% and 81% agreement respectively from the Delphi consensus panel.

e. **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.** ***(Strong recommendation, Delphi consensus (100%))***

f. **Offer lifelong follow-up for evolving hypopituitarism with the frequency determined on an individual patient basis.** ***(Strong recommendation, Delphi consensus (100%))***

Individual authors advocate different endocrine screening methods and intervals after treatment with no consensus on best practice, apart from agreeing that lifelong endocrine follow-up to screen for and manage hypothalamic, anterior and posterior pituitary deficits is required. After growth completion, transition to specialist adult neuroendocrine services should be effected and individually tailored. These statements both achieved 100% agreement with the Delphi consensus panel.

Recovery of hypothalamo-pituitary function is reportedly uncommon after surgery, the evolution of new deficiencies over time being more usual (22, 24, 32, 242), although a few retrospective studies in CYP report rare recovery of pre-operative hypoadrenalism and hypothyroidism (243). In this latter report, however, it was difficult to ascertain whether the pre-operative hypoadrenalism was due to perioperative glucocorticoid-induced adrenal suppression rather than true ACTH deficiency (see section 3.2.2.5.h). Whilst CDI can be transient in the postoperative period (see section 3.2.2.2.c), new or persistent central DI (present >1 month postoperatively) can occur in up to 70-93% of patients, and in almost all patients (up to 100%) undergoing radical resection of their tumour (177, 244, 245). Other predictors of persistent CDI include recurrent surgery, pituitary stalk injury and a transcranial approach, although the most significant risk factor is the surgeon's operative goal of GTR of the tumour mass (177).

g. **Consider recombinant human growth hormone (rhGH) therapy 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.** ***(Moderate recommendation, moderate quality of evidence)***

A wide variety of studies including interrogation of post-marketing surveillance databases, cohort studies and case series involving many patient-years of observation show no evidence that rhGH treatment in replacement doses increases the background recognised relapse rate of brain tumours. Prospective cohort and case-control studies in patients with craniopharyngioma with and without rhGH therapy followed-up for 3-10 years have shown no independent impact of rhGH therapy on PFS and event-free survival (134, 246, 247). In one retrospective case-control study, four patients with craniopharyngioma treated with rhGH for a mean of 6.3 (range 0.8-22) years developed tumour recurrence over a 10.8 (range 1.9-40) year follow-up as compared to 22 GH-naïve patients, and rhGH was not an independent predictor of recurrence on multivariate analysis, even when accounting for the duration of treatment (248). Another retrospective study showed no increased tumour recurrence rate in patients who had received radiotherapy and rhGH (249). These findings are in keeping with those of two larger studies of childhood brain tumours and childhood cancer, although both excluded craniopharyngiomas from their patient cohorts (250, 251).

Pharmacovigilance retrospective cohort studies with historical controls also do not support an association between rhGH therapy and tumour recurrence. The National Cooperative Growth Study (NCGS) reported a recurrence rate of 6.4% in patients with craniopharyngiomas on rhGH therapy (252, 253) and the KIGS post-marketing surveillance studies in 1038 patients with craniopharyngiomas (adults and children) receiving rhGH suggest recurrence rates of 11.7% and a 10-year PFS of 64% with no effect of rhGH dose or timing of rhGH commencement within 5 years of diagnosis (254). However, such studies are prone to selection bias, especially the practice to delay rhGH therapy for 1-2 years, and neither database specifically set out to look for tumour recurrence, so there is no direct non-treated control group which might inform this.

The American Lawrence-Wilkins Paediatric Endocrine Society and Endocrine Society guidelines recommend initiating rhGH 1 year after completion of any brain tumour treatment, but this is based on little substantive evidence (255-257). The restoration of musculoskeletal and metabolic wellbeing is paramount in CYP with craniopharyngiomas, who often present with panhypopituitarism, which may mandate prompt therapy from diagnosis. Indeed, the most recent guidance indicates that rhGH can be commenced in CYP with craniopharyngiomas from as early as 0.7 years from diagnosis (257), particularly as concerns that it may precipitate recurrence or second neoplasms remain unfounded. Prompt re-establishment of normal linear growth and limiting obesity, which can occur in the face of GH deficiency with appropriate titration of rhGH doses should be considered one of the aims of endocrine management of survivors.

h. **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.** ***(Strong recommendation, Delphi consensus (100%))***

Early assessment of pituitary ACTH reserve, whether after perioperative dexamethasone for cerebral oedema or prophylactic hydrocortisone cover, should be performed within 6 weeks of surgery (see Section 3.2.2.5.e) to assess the possibility of new ACTH deficiency as distinct from ACTH suppression and recovery. Dynamic insulin tolerance or low dose synacthen stimulation combined with serial morning cortisol and ACTH measurements may be required to assess adrenal recovery the possibility of adrenal recovery at intervals even many years later. In the absence of high quality evidence, the above statement was put to the Delphi consensus panel and achieved 100% agreement in the 2nd round.

i. **Consider access to a designated MDT with specialist dietary, exercise, psychological and endocrine input for the management of hypothalamic obesity.** ***(Moderate recommendation, moderate quality of evidence)***

The pathophysiology of hypothalamic obesity is multifactorial with no single effective and safe intervention. Studies have included small numbers of patients with short periods of follow-up, utilising pharmacological agents such as triiodothyronine (258, 259), octreotide (260, 261), dextroamphetamine (262, 263), methylphenidate (264), sibutramine (265), and more recently GLP-1 agonists such as exenatide and liraglutide (266-268). One prospective, randomised, double-blind, placebo-controlled trial of octreotide in 9 patients reported a slight change in BMI of -0.2 ± 0.2 kg/m^2 compared with +2.2 ± 0.5 in 9 controls at 6 months, but long-term outcomes remain unknown more than 10 years later (260). The only randomised double-blind placebo-controlled crossover trial of sibutramine in hypothalamic obesity showed both intervention arms reduced by BMI SDS by -0.68 and -0.72 compared with -0.06 and +0.43 SDS in the placebo arms respectively (265). However both these agents have long-term side effects which limit their use, especially in CYP. Sibutramine has now been withdrawn due to cardiovascular side effects, whilst octreotide (260) and triiodothyronine (258) disrupt glucose tolerance and euthyroidism and bone health respectively. One study of 33 CYP with craniopharyngiomas aged 7.6 years at diagnosis and 13.4 years at first multidisciplinary obesity clinic visit demonstrated that they gained less weight over 12 months than in standard care (+8.5%/ year vs. +21.4%/ year), and reported improved health-related quality of life (269).

A systematic review and pooled meta-analyses of 21 craniopharyngioma patients undergoing various types of bariatric surgery showed a weight loss of -20.9 kg (95% CI -35.4 to -6.3) at 6 months and -15.1 (95% CI -31.7 to +1.4) kg at 12 months, as well as a reduction in the proportion of patients with type 2 diabetes from 31.6% to 7.1% and 8.3% at 6 and 12 months respectively (270). The risk-benefit of performing such surgery in CYP with morbid obesity and life-threatening hypopituitarism, as well as the longevity of weight loss which appears to reduce with time, requires careful decision-making in the context of an MDT. Given its severe detriment on clinical well-being and the absence of an effective safe intervention for morbid hypothalamic obesity, neurosurgical strategies to preserve hypothalamic integrity and timely hormone replacement are mandatory for its prevention.

j. **Be aware of specialist sleep laboratory and behavioural neuropsychopharmacology services for CYP with hypothalamic injury and disturbed sleep and/ or behaviour.** ***(Weak recommendation, low quality of evidence)***

Sleep disorders are increasingly prevalent in long-term survivors of paediatric craniopharyngiomas, with 12% of children affected at a median 10 years after surgery (271). Several studies show increased sleep-disordered breathing and sleep fragmentation, less sleep efficiency, REM sleep, sleep onset latency and reduced oxygen saturation and an increased obstructive apnoea-hypopnoea index compared with weight-matched controls (272-276). Increased daytime sleepiness affects CYP with craniopharyngioma with a higher BMI, whilst a history of irradiation was correlated with lower melatonin concentrations, higher Epworth Sleepiness Scale scores and the presence of central or obstructive sleep apnoea on polysomnography (112, 274, 275, 277-282). The stimulants modafinil, methylphenidate, dextroamphetamine and the sedative melatonin have tried in single-arm studies (262, 274, 282-284), but their efficacy and safety requires further study. Referral to specialist sleep laboratories is therefore recommended. A neurosurgical strategy that preserves hypothalamic integrity has been advocated to reduce such sleep disorders (284), although this was not confirmed to be efficacious in one study (277).

k. **Offer interval neuropsychological assessments until adulthood to inform clinical and educational neurorehabilitation and vocation in CYP with identified neuropsychological and**

neurological deficits (e.g. seizures, stroke, visual impairment) and those who have undergone cranial radiotherapy. *(Strong recommendation, Delphi consensus (100%))*

Our literature review suggests that both craniopharyngioma and its treatment are risk factors for neuropsychological impairment. Many single centre uncontrolled studies outline the wide variety of deficits faced by CYP with craniopharyngioma. Given the large quantity of literature and the changing surgical and radiotherapeutic strategies over time, the GDG did not review any published articles more than 20 years ago. Since methods of neuropsychological and psychosocial assessment varied significantly between studies, the GDG could not make a recommendation as to the best method(s) of assessment.

Several studies of CYP treated for craniopharyngiomas report some degree of broadly-conceived cognitive, emotional, psychosocial and/or educational deficits, sometimes linked to a hypothalamic syndrome (24, 26, 34, 131, 271, 285-299). Furthermore, several studies indicate that even if measures of general intelligence might be within the normal to low-normal range (290, 300, 301), specific deficits could be identified in visual-spatial cognition (302, 303), memory (23, 26, 290, 300, 302, 304-307), executive function (302, 307-310), and emotion/ behaviour (292, 311). Other studies suggest that relatively conservative surgical procedures combined with radiotherapy reduced the risk of neuropsychological impairment compared to more extensive resection (25, 296, 308, 312-314). However, radiotherapy was also linked to behavioural and social impairments in two papers (315, 316). Additionally, multiple recurrent interventions increased the likelihood of cognitive impairment (289, 317), whilst tumour position may play a role in psychosocial and behavioural problems (294).

There is therefore no doubt that systematic and comprehensive longitudinal assessment of general psychological functioning and specific neuropsychological domains will be necessary to describe adequately the sequelae of craniopharyngiomas and their treatment. However, given the lack of evidence of which patients should be prioritised for assessment, and which method of assessment should be used, the above recommendation was put to a panel of Delphi consensus experts, and achieved 100% agreement. Despite this, these recommendations do not preclude the need for consideration of neuropsychological follow-up of CYP with craniopharyngiomas who have only undergone surgical resection without radiotherapy.

3.2.2.6 Management of recurrence

a. Offer further surgery before radiotherapy to avoid or reduce the radiation field before radiotherapy CYP with cystic and/ or solid recurrences after a radiologically complete resection without previous irradiation. *(Strong recommendation, Delphi consensus (100%))*

b. Offer further cyst drainage before radiotherapy in CYP with progressive, primarily cystic recurrences following initial incomplete resection without radiotherapy. *(Strong recommendation, Delphi consensus (100%))*

c. Offer radiotherapy with further surgery to reduce the radiation field in CYP with progressive, primarily solid recurrences following initial incomplete resection without radiotherapy. *(Strong recommendation, Delphi consensus (100%))*

d. Offer a repeat course of conventional radiotherapy for the treatment of disease progression or recurrence after previous radiotherapy only in exceptional cases and only after all other therapeutic modalities have been explored, given its high morbidity. *(Strong recommendation, Delphi consensus (100%))*

The treatment of recurrent or progressive tumours remains a significant challenge and is a matter of debate as all available evidence is of low quality. There is some evidence that the timing of radiotherapy (early adjuvant vs. salvage at recurrence) does not significantly affect

survival outcomes despite evidence for its efficacy in stabilising tumours, potentially with an impact on morbidity (see section 3.2.2.3.c). The few small volume studies that address treatment for recurrence do not dissect out outcomes based on the treatment modality used for primary and recurrent tumours (22, 141, 225, 301, 318-322). Two studies demonstrate a higher rate of second recurrence if radiotherapy is omitted from the second line treatment strategy – 5-year post-recurrence PFS was 80% after STR and radiotherapy, but only 50% and 16% in patients after just GTR and STR respectively (323). Kalapurakal et al.(2000) also demonstrated a 100% 5-year post-recurrence PFS with radiotherapy and 0% without, with a median post-operative time to second relapse of 12 (range 2-36) months (318). No patient in either of these studies had received primary radiotherapy. These data suggest radiation at relapse would be better at stabilising disease and may prevent further morbidity, especially as repeated surgery and difficulties in achieving GTR (321) have been associated with poorer functional outcomes (322).

However, there is some evidence for the size of cystic craniopharyngiomas affecting the radiotherapeutic response, suggesting that primarily cystic progressions or recurrences should have been aspirated and reduced before irradiation to the whole tumour volume, especially as this is a relatively minor intervention compared with definitive resection. By contrast, a solid tumour previously not amenable to GTR is unlikely to be completely resectable at recurrence without a significant impact on morbidity, and hence radiation should be administered in naïve patients, although surgery to reduce the solid component and thus the radiation field can be considered.

In patients with post-radiation solid recurrence, second course radiotherapy is not commonly offered, particularly given the risk of exceeding optic chiasm dose constraints and the potential risk of neurotoxicity on the developing brain (324, 325), and would need very careful consideration by the MDT.

The Delphi consensus panel considered each of the above recommendations and achieved 100%, 100%, 93% and 100% agreement to this approach. Given the lack of evidence in this area, teams managing CYP with recurrent/ relapsed craniopharyngiomas should be aware of current trials in this area, and consider offering opportunities for participation where clinically appropriate.

e. **Be aware that gamma knife radiosurgery for recurrent or progressive craniopharyngiomas should only be considered in a research setting as there is currently insufficient evidence for its efficacy.** ***(Weak recommendation, low quality of evidence)***

All the studies of SRS use at recurrence of craniopharyngiomas are of low quality, consisting of mixed adult and paediatric uncontrolled cohorts in single centres without subcohort analysis by age (206, 212, 213, 215, 323, 326-328). One study showed similar mean PFS for SRS as for conventional radiotherapy (1907 (95% CI 1261-2552) days vs. 2816 (95% CI 2070-3561) days), but only 48% of tumours in this study were recurrent (327). Another study showed similar 5-year PFS for recurrent tumours after SRS vs. STR with adjuvant radiotherapy (83% vs. 80%), both of which were better than STR alone (16%) (323). Additionally, visual deterioration and poorer long-term functional status was less likely after SRS or STR with adjuvant radiotherapy than after STR alone. Given the absence of comparative studies of SRS vs. conventional radiation in CYP, the GDG did not feel it could recommend SRS as a primary treatment option for recurrent disease. However, the available data suggest that stereotactic radiosurgery has a good response rate and a favourable risk profile, particularly for small tumour volumes <1.6 cm^3 (especially away from the optic pathway) where complete coverage of the tumour mass by the radiation dose is achieved (206, 213, 328), therefore worthy of further study of effectiveness and long-term toxicity in this cohort.

f. Be aware that repeated courses of intracystic IFNα via an indwelling catheter could be considered instead of aspiration alone in CYP with recurrent cystic craniopharyngiomas. *(Weak recommendation, low quality of evidence)*

Different intracavitary treatments for recurrent cystic craniopharyngiomas have been reported in institutional case series (224-226, 228, 230, 329-331), with a more recent focus on intracystic IFNα and a parallel reduction in the use of intracystic bleomycin and brachytherapy. Section 3.2.2.4.a details the evidence for intracystic therapies with no added information gained in our search for cystic recurrences, outcomes being difficult to separate from primary and more conventional treatment strategies (224-226, 332). Cyst volume reductions of between 24.8-88.3% have been reported with a 5-year in-field PFS approaching 81% in some cohort studies (329, 330).

g. Be aware that systemic IFNα in CYP with recurrent craniopharyngiomas should only be considered in the context of a research trial as there is currently insufficient evidence for its efficacy. *(Weak recommendation, low quality of evidence)*

Three small uncontrolled cohort studies report some effect of systemic IFNα-2a or pegylated IFNα-2b in patients with recurrent/ cystic progressive craniopharyngiomas, with stabilisation or reduction in cystic disease, some of whom exhibited sustained tumour responses over time (236, 237, 333). However, given the significant side effects of systemic therapy (fever, neutropenia, transaminitis, fatigue, rashes, seizures, insomnia, anxiety) (236), particularly in a vulnerable population with potential hypopituitarism, systemic IFNα requires further study and should not be administered to CYP outside the context of a clinical trial.

4. Implementation, evaluation & audit

In addition to publishing the electronic version of this guideline together with the other seven guidelines in this series on the main CCLG website, providing electronic cross references between them and linking all of these to the BSPED and RCPCH websites, we will also disseminate them widely to all the stakeholder groups and offer similar electronic links. We have already presented abstracts of this guideline at the International Meeting of Paediatric Endocrinology (2017) and the International Society of Paediatric Neuro-oncology Symposium (2018), the Royal College of Paediatrics & Child Health Conference (2018), the European Society for Paediatric Endocrinology Annual Meeting (2019), the British Society for Paediatric Endocrinology & Diabetes Annual Meeting (2019) and will be planning keynote focus presentations at the annual conferences of both the CCLG and BSPED societies and publication of peer reviewed summary guideline articles, either as a series or a supplement, in a high impact speciality journal.

4.1 Barriers, facilitators and resource implications

Implementation of this, and each of the other seven guidelines in this series, will be subject to evaluation. We aim to effect prospective central registration of each patient via the CCLG's already streamlined system of centre coordinators who undertake this for all children with cancers treated at the UK's 16 CCLG accredited tertiary centres. The CCLG will also explore the possibility of an automated electronic link to the web-based guidelines, which would provide both a record of those using the guideline and facilitate a voluntary data retrieval system for evaluation of both professional experience and patient treatment outcomes, at 2- to 3-year intervals. This will help achieve greater uniformity in the management of CYP with craniopharyngiomas nationally, and will highlight potential areas where service provision is inadequate.

Development of this guideline was aimed at defining a standard of best practice, with the awareness that existent infrastructure in some centres would already fall short of the standards described here. The GDG recognises that some of the recommendations within this guideline will require a degree of service reorganisation, and also that a significant proportion of this guideline is based on low quality evidence or expert consensus. Access to all of the appropriate members of the MDT recommended in this guideline for the care of CYP with craniopharyngioma may not always be available in all sites currently managing such patients, and this guidelines aims to provide a standard against which such care can be audited to make a case for improving existing infrastructure and facilities. Centralisation of the management of such cases may however result in cost and resource savings by avoiding duplication and reducing the likelihood of poorer outcomes when managed in smaller, less experienced centres(39). It is therefore imperative to create a centralised system for long-term outcome data collection to ensure the guideline recommendations and their outcomes, benefits and risks to CYP with craniopharyngiomas are fully audited and understood.

4.2 Audit criteria

The following key areas of recommendation will be audited:

- Management of CYP with craniopharyngiomas in specialist centres with adequate multidisciplinary team support experienced in treating these tumours
- The use of the hypothalamic grading system as part of comprehensive neuroradiological and neurosurgical assessment to assess the risk of future hypothalamic damage prior to any surgical and/ or radiotherapeutic intervention
- Evidence for a risk-based approach to surgical resection
- Adequate perioperative endocrine management with the involvement of a paediatric endocrinologist
- Appropriate use of radiotherapy, including access to proton beam therapy, to optimise overall and progression-free survival
- Comprehensive pre- and post-treatment assessment of endocrine, visual and neurocognitive function
- Adequate, comprehensive planning for transition of care to adult services.

5. Conclusions

The rarity of paediatric endocrine tumours such as craniopharyngiomas makes their management challenging. There have been repeated calls by multidisciplinary professionals caring for these children for these society-commissioned, RCPCH-endorsed, evidence-based and high quality consensus guidelines since the original 2005 consensus recommendations, which were previously well-received by both users and patient groups alike. During the process of guideline development, we have confirmed a general lack of high quality evidence relating to this age group and identified, through the Delphi consensus surveys, the need to develop multispecialty advisory panels (e.g. currently operating informally as the Hypothalamo-Pituitary Axis Tumour (HPAT) advisory group), particularly for complex cases, and most importantly, a national register for evaluation of key management outcomes in these rare, eminently curable, young, survivor cohorts. This is crucial to inform clinical trials, enhance the quality of evidence, potentially improve health-related quality of survival and improve equity of access to expert care.

6. Updating the recommendations

The literature will be reviewed five years after guideline publication. If relevant new evidence is identified sooner than/ before five years the GDG will update the guideline (or appropriate section) according to the evidence identified.

7. Glossary

ACTH	Adrenocorticotrophic hormone
ADC	Apparent diffusion coefficient
ADH	Antidiuretic hormone (also arginine-vasopressin (AVP))
AFP	α-fetoprotein
ANP	Atrial natriuretic peptide
β-hCG	β-human chorionic gonadotrophin
BMI	Body mass index
BNP	Brain natriuretic peptide
BSPED	British Society for Paediatric Endocrinology & Diabetes
CCLG	Children's Cancer and Leukaemia Group
CI	Confidence interval
CRH	Corticotrophin-releasing hormone
CSF	Cerebrospinal fluid
CT	Computerised tomography
CTV	Clinical target volume
CYP	Children and young people (<19 years of age)
DI	Diabetes insipidus
DTI	Diffusion-tensor imaging
DWI	Diffusion-weighted imaging
FSH	Follicle-stimulating hormone
GDG	Guideline Development Group
GH	Growth hormone
GTR	Gross total resection (also complete resection)
GTV	Gross tumour volume
HR	Hazard ratio
IFNα	Interferon-α
IGF-1	Insulin-like growth factor 1
LDST	Low-dose synacthen test
LH	Luteinising hormone
LHRH	Luteinising hormone-releasing hormone (also gonadotrophin-releasing hormone (GnRH))
MDT	Multidisciplinary team
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
NICE	National Institute for Care and Health Excellence
OCT	Optical coherence tomography
OS	Overall survival
PBT	Proton beam therapy
PICO	Population, Intervention, Comparison, Outcome (question format)
PFS	Progression-free survival (also recurrence-free survival)
POSCU	Paediatric oncology supportive care unit
PROPELLER	Periodically rotated overlapping parallel lines with enhanced reconstruction (DWI technique)
PWI	Perfusion-weighted imaging
RCPCH	Royal College of Paediatrics & Child Health
rhGH	Recombinant human growth hormone
SIADH	Syndrome of inappropriate antidiuretic hormone secretion
SDS	Standard deviation score
SRS	Stereotactic radiosurgery
SST	Standard synacthen test
STR	Subtotal resection (also incomplete/ partial resection)
T_4	Thyroxine (thyroid hormone)
TRH	Thyrotrophin-releasing hormone
TSH	Thyroid-stimulating hormone (also thyrotrophin)

VA	Visual acuity
VEP	Visual evoked potential
VF	Visual field

8. Relevant associated guidelines

- CCLG Brain Tumour Imaging Protocol (46)
- Growth Hormone Research Society Consensus Guidelines for the Diagnoses and Treatment of Growth Hormone Deficiency in Childhood and Adolescence (74)
- European Thyroid Association Guidelines on the Diagnosis and Management of Central Hypothyroidism (85)
- Pediatric Endocrine Society Guidelines for Growth Hormone and Insulin-Like Growth Factor-1 Treatment in Children and Adolescents (256)
- Endocrine Society Clinical Practice Guideline for Hypothalamo-Pituitary and Growth Disorders in Survivors of Childhood Cancer (257)

9. Acknowledgments

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10. Appendices

Appendix A

Declaration of conflicts of interest

All GDG and Delphi consensus group participants were asked to declare any conflicts of interests as per the NICE conflicts of interest policy (https://www.nice.org.uk/about/who-we-are/policies-and-procedures). Apart from those listed below, all other members of the GDG and Delphi consensus panel declared no conflicts of interest.

- Dr Gan has received educational grants and had travel expenses and hospitality paid for by Ipsen Ltd., Pfizer Ltd., Sandoz Ltd. and Novo Nordisk Ltd. for various national and international meetings. He has received speaker fees from Ipsen Ltd. and Novo Nordisk Ltd. He is also a member of the SUCCESS Charity steering committee.
- Dr Albanese does consultancy work for Pfizer Ltd., Novo Nordisk Ltd., Ferring Pharmaceuticals Ltd., Eli Lilly and Company Ltd. and Sandoz Ltd. She has also been invited so speak on behalf of Ferring Pharmaceuticals Ltd., Sandoz Ltd. and Novo Nordisk Ltd. and has had travel expenses and hospitality provided by Ferring Pharmaceuticals Ltd., Merck Serono Ltd., Novo Nordisk Ltd., Sandoz Ltd., Ipsen Ltd., Pfizer Ltd., Alexion Pharma UK Ltd., and the Menarini Foundation to attend national and international meetings.
- Professor Jacques is the company secretary, director and shareholder in Repath Ltd., a private pathology company. He is also a director and shareholder in Neuropath Ltd., a private pathology company. He is the editor-in-chief of the journal Neuropathology and Applied Biology. He is the lead of the childhood solid tumour domain of the Genomes England Clinical Interpretation Partnership (GECIP). He is a member of the Financial and General Planning Committee of the British Neuropathological Society.
- Professor Korbonits has received grant funding from Pfizer Ltd., Crinetics Pharmaceuticals Inc. and ONO Pharma UK Ltd., and accepted speaker fees from Novo Nordisk Ltd., Ipsen Ltd. and Pfizer Ltd. She was on the advisory board of Recordati S.p.A and Novo Nordisk Ltd .

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Appendix B: Summary of methods used to develop the guidance

Methods

This guideline was developed in accordance with The Appraisal of Guidelines Research and Evaluation Instrument II (AGREE II) criteria (334) and the Children's Cancer and Leukaemia (CCLG) guideline development standard operating procedure, version 5 (335). The methodology is summarised in figure 1. All stages of the guideline development process were overseen and approved by the Quality Improvement Committee of the RCPCH.

The guideline development group (GDG) identified the guideline objectives which were summarised as a series of PICO clinical questions. The guideline objectives and clinical questions were reviewed by previously identified guideline stakeholders to ensure no relevant area had been omitted. The clinical questions were used to direct a systematic literature search. Titles and abstracts identified in the literature search were screened by the GDG and full text articles relevant to guideline development reviewed. The quality of evidence identified in the systematic search was appraised using the GRADE criteria(1).

Where the literature search identified evidence to answer the PICO questions, the guideline development group made a guideline recommendation. The strength of the recommendation was determined by the trade-off between the benefits and harms of the recommendation, taking into account the quality of the underpinning evidence. Recommendations which were based on existing low quality evidence, but were deemed unlikely to be further researched in higher quality studies due to already being in common, widespread practice were strengthened by internal GDG consensus. Where there was no/ insufficient evidence, or the identified evidence was contradictory, the GDG drafted recommendations based on their expert opinion. Recommendations based on GDG expert opinion alone were peer reviewed using a formal consensus process (Delphi process) (2). All members of the Delphi consensus panel were allowed to vote for all proposed recommendations. A recommendation was deemed to have achieved consensus if 70% or more of the Delphi respondents supported the recommendation. All recommendations were reviewed by the guideline stakeholders and at least one selected peer expert, prior to guideline publication.

All GDG and Delphi consensus group participants were asked to declare any conflicts of interests as per the NICE conflicts of interest policy (https://www.nice.org.uk/about/who-we-are/policies-and-procedures). The guideline development was sponsored by unrestricted grants from Sandoz Pharmaceuticals, the patient support groups AMEND and The Pituitary Foundation, and the professional societies, The British Society of Neurosurgeons, CCLG and BSPED. Excepting as stakeholders (excluding Sandoz), the sponsors had no role in development of guideline methodology or final guideline recommendations. The CCLG provided administrative support throughout the guideline and the RCPCH provided advice and assessed it at different stage to ensure it met AGREE II requirements.

Figure 1: Guideline development process

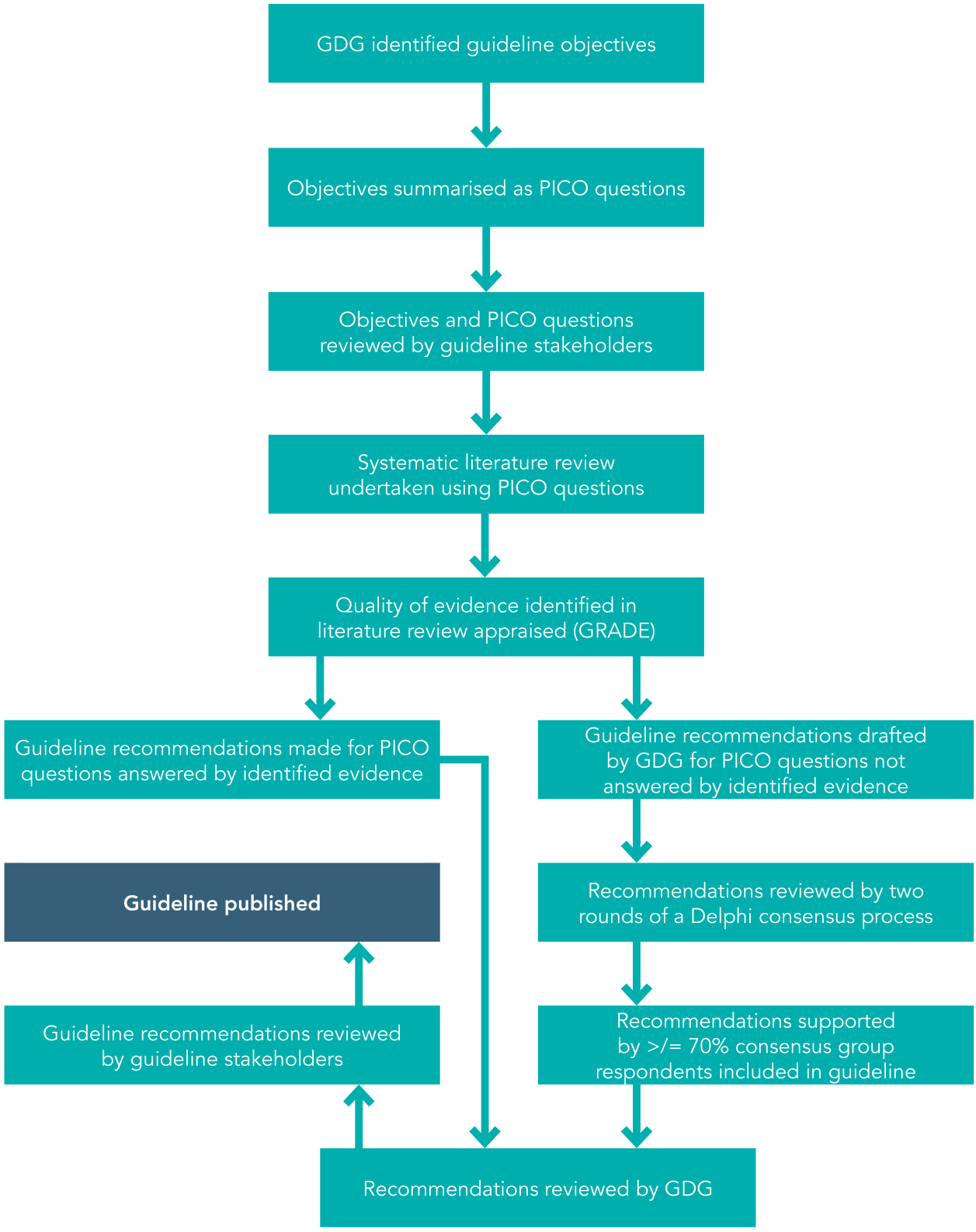
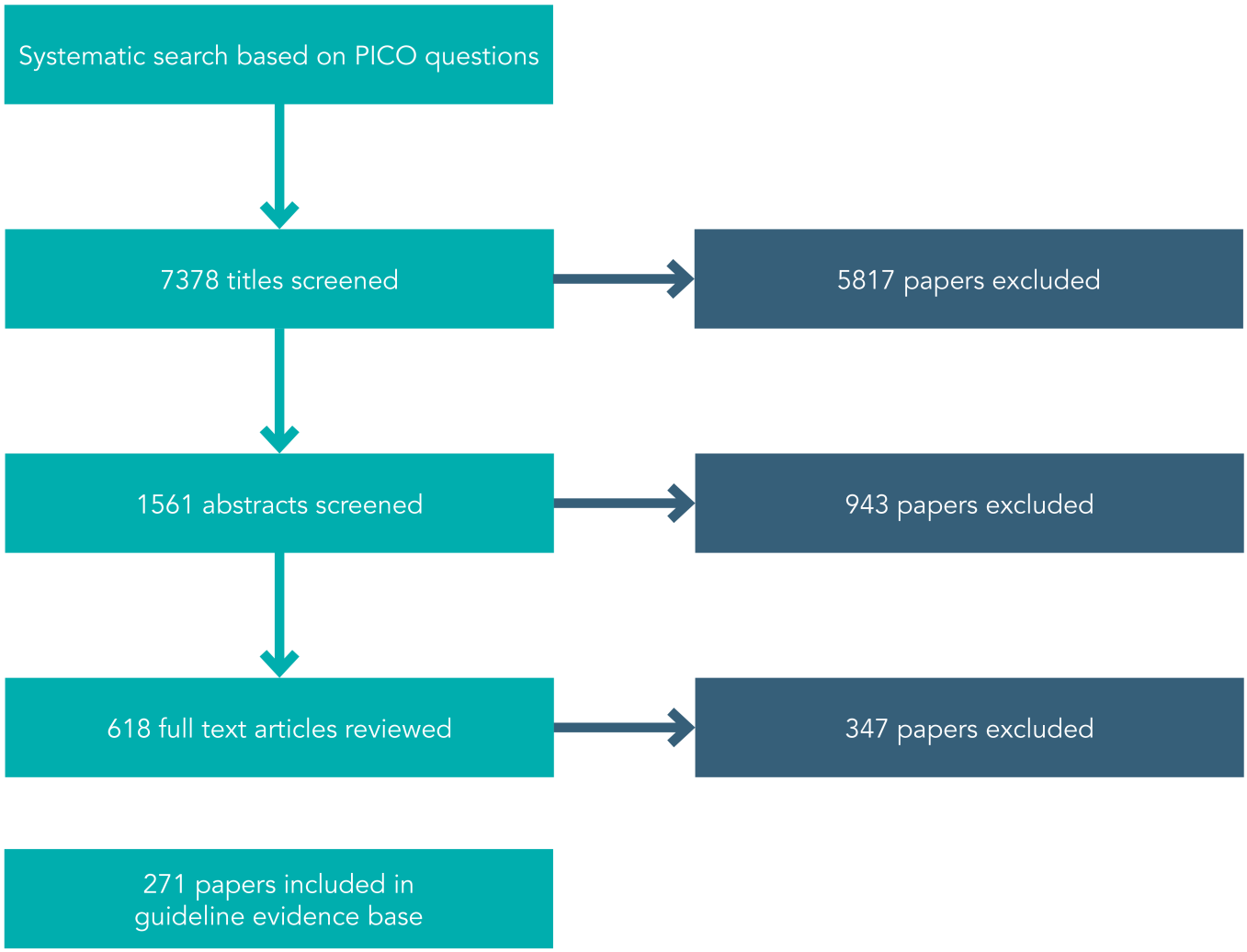


Figure 2: Literature review process (note that the number of papers excluded at each stafe are illustrated for individual PICO questions in the tables that follow)



Appendix C: The evidence

Outcome 3.1.2.b: Management in tertiary paediatric specialist centres by a multidisciplinary team

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years with craniopharyngiomas **I** does a policy for management in tertiary specialist centres with multidisciplinary team support (e.g. neurosurgery, radiation oncology, endocrinology, neuroradiology, neuropathology) **C** compared to no policy for such management (i.e. management by any team in any hospital) **O** improve overall and progression-free survival?	1. exp Craniopharyngioma/ or craniopharyngioma*.mp. 2. limit 1 to "all child (0 to 18 years)" 3. Patient Care Team/ or multidisciplinary.mp. 4. MDT.mp. 5. (tertiary or specialist*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 6. 3 or 4 or 5 7. 2 and 6	75	28	9	1

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Muller et al., 2011(39)	Prospective cohort	Yes: Large centres less likely to aim for complete resection, and small centres more likely to have lesions with more hypothalamic involvement, no multivariate analysis performed on hypothalamic outcome	No	No	No	Yes: Only neurosurgical centres included	No	No	Yes: Rate of hypothalamic lesions increased from large to small centres

Author(s)	Summary of findings					Quality
	No. of events in small centre	No. of patients	No. of events in large centre	No. of patients	Pooled effect	
Muller et al., 2011	20	23	17	34	RR small vs. large 1.7 (1.2-2.5)	Very low

Outcome 3.2.1.1.a: Sensitivity and specificity CT imaging in addition to MRI at diagnosis

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years with craniopharyngiomas how does **I** CT imaging in addition to MRI compare to **C** MRI alone **O** in terms of sensitivity and specificity for diagnosis?	1. exp Craniopharyngioma/ or craniopharyngioma*.mp. 2. limit 1 to "all child (0 to 18 years)" 3. exp Magnetic Resonance Imaging/ or MRI.mp. 4. Tomography, X-Ray Computed/ or CT.mp. 5. 2 and 3 and 4	218	149	15	5

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Zhou et al., 2009(40)	Retrospective cohort	Yes – only included posterior fossa craniopharyngiomas	No	Yes – mixed cohort of adults and children (5/7 CYP)	Yes – very small cohort of 7 patients	No	No	No	No
Molla et al., 2002(10)	Retrospective cohort	Yes – unclear blinding by radiologists	No	Yes – mixed cohort of adults and children (mean 29 years)	Yes – relatively small cohort of 26 patients	No	No	No	No
Zhang et al., 2002(11)	Retrospective cohort	Yes – unclear blinding by radiologists	No	No	No	No	No	Yes – large cohort of craniopharyngiomas of both histological subtypes	No
Tsuda et al., 1997(41)	Retrospective cohort	Yes – unclear blinding by radiologists	No	Yes – mixed cohort of adults and children (7/20 children)	Yes – relatively small cohort of 20 patients	No	No	No	No
Eldevik et al., 1996(42)	Retrospective cohort	Yes – unclear blinding by radiologists, unclear how CT vs. MRI modalities were decided/ performed	No	Yes – mixed cohort of adults and children (22/45 <20 years)	Yes – relatively small subcohort of 22 paediatric patients	No	No	No	No

Author(s)	Summary of findings					Quality
	Positive identification by calcification seen on CT	No. of patients	Positive identification by T_1/T_2-weighted signal intensity on MRI	No. of patients	Pooled effect	
Zhou et al., 2009	4	7	T_1-weighted hypointensity 5 T_2-weighted hyperintensity 7 Contrast enhancement	7	N/A	Very low

Author(s)	Summary of findings					Quality
	Positive identification by calcification seen on CT	No. of patients	Positive identification by T_1/T_2-weighted signal intensity on MRI	No. of patients	Pooled effect	
Molla et al., 2002	17	26	Mixed solid + cystic components 24 T_1-very hyperintense, T_2-very hyperintense (blood-like) 5 T_1-mildly hyperintense, T_2-very hyperintense (protein-like) 14 T_1- very hyperintense, T_2- hyperintense (fatty) 4 T_1-hypointense, T_2-very hyperintense (CSF-like) 6 All four patterns 5	26	N/A	Very low
Zhang et al., 2002	176	187	Mixed solid + cystic components 187	187	N/A	Low
Tsuda et al., 1997	Correct diagnosis 14 Calcification 10	18	Correct diagnosis 16 Mixed solid + cystic components 16 Cystic only 3 Solid only 1 T_2-hyperintensity 19 T_1-hypointensity 10	20	1/14 CT-identified cases wrongly diagnosed by MRI	Very low
Eldevik et al., 1996	Calcification 21	22	Mixed solid + cystic components 19 Cystic only 3	22	N/A	Very low

Outcome 3.2.1.1.b: Sensitivity and specificity of new multimodal imaging techniques at diagnosis

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years with craniopharyngiomas how do **I** recent MRI imaging techniques such as DWI, DTI, perfusion scanning, spectroscopy, 3+T scanning **C** in comparison to standard imaging techniques (T1/2-weighted imaging with contrast) **O** in terms of overall sensitivity and specificity for diagnosis?	1. exp Craniopharyngioma/ or craniopharyngioma*.mp. 2. limit 1 to "all child (0 to 18 years)" 3. exp Magnetic Resonance Imaging/ or MRI.mp. 4. (sensitivity or specificity).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 5. 3 and 4 6. 2 and 5	12	9	5	3 (insufficient data therefore Delphi consensus)

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Yeom et al., 2014(47)	Retrospective cohort	Yes – no comparison to conventional imaging	No	Yes – mixed cohort of tumours (4/54 craniopharyngiomas)	Yes – only small subcohort of 4 craniopharyngiomas	No	No	No	No
Mahmoud et al., 2010(48)	Retrospective cohort	Yes – excluded lesions <10mm	No	Yes – mixed cohort of adults and children (mean age 49.5 years), mixed cohort of tumours (5/60 craniopharyngiomas)	Yes – only small subcohort of 5 craniopharyngiomas	No	No	No	No
Kunii et al., 2007(49)	Retrospective cohort	Yes – no comparison to conventional imaging	No	Yes – mixed cohort of adults and children (mean 45.8 years), mixed cohort of tumours (6/29 craniopharyngioma)	Yes – only small subcohort of 6 craniopharyngiomas	No	No	No	No

Author(s)	Summary of findings					Quality
	Parameters in craniopharyngioma goup	No. of patients	Parameters in non-craniopharyngioma group	No. of patients	Pooled effect	
Yeom et al., 2014	Relative tumour blood flow (rTBF) 0.99 ± 0.13	4	<u>Relative tumour blood flow (rTBF):</u> Hypothalamic astrocytoma 0.99 Thalamic PNET 1.32 Optic chiasm glioma 0.80 ± 0.09		High grade tumours had higher rTBF compared to low-grade tumours, but within tumour grades individual histologic subtypes not distinguishable	Very low

Author(s)	Summary of findings					Quality
	Parameters in craniopharyngioma goup	No. of patients	Parameters in non-craniopharyngioma group	No. of patients	Pooled effect	
Mahmoud et al., 2010	T_1-weighted mean signal intensity 1.13 ± 0.18 T_2-weighted mean signal intensity 1.73 ± 0.44 Degree of enhancement 1.17 ± 0.08 Mean ADC 1.97 ± 0.54	5	T_1-weighted mean signal intensity Pituitary adenoma 0.89 ± 0.12 Rathke's cleft cyst 1.29 ± 0.38 Parasellar meningioma 0.88 ± 0.08 T_2-weighted mean signal intensity Pituitary adenoma 1.46 ± 0.35 Rathke's cleft cyst 1.78 ± 0.42 Parasellar meningioma 1.36 ± 0.17 Degree of enhancement: Pituitary adenoma 1.99 ± 0.36 Rathke's cleft cyst 1.11 ± 0.09 Parasellar meningioma 1.99 ± 0.42 Mean ADC: Pituitary adenoma 1.08 ± 0.19 Rathke's cleft cyst 2.02 ± 0.45 Parasellar meningioma 0.84 ± 0.10	 24 10 7 24 10 7 24 10 7	Accuracy of conventional MRI: Haemorrhagic pituitary adenomas vs. craniopharyngiomas 94.7% Accuracy of conventional MRI + minimum ADC: Haemorrhagic pituitary adenomas vs. craniopharyngiomas 100% Accuracy of minimum ADC: Craniopharyngiomas vs. Rathke's cleft cyst 100%	Very low
Kunii et al., 2007	Mean ADC 1.41 ± 0.34 Mean relative ADC 1.62 ± 0.28	6	Mean ADC: Rathke's cleft cyst 2.12 ± 0.29 Cystic pituitary adenoma 2.27 ± 0.20 Mean relative ADC: Rathke's cleft cyst 2.61 ± 0.37 Cystic pituitary adenoma 2.72 ± 0.17	 12 6 12 6	Significantly higher ADC and relative ADC in Rathke's cleft cysts vs. craniopharyngioma cysts	Very low

Outcome 3.2.1.1.c: Sensitivity of hypothalamic grading systems on predicting future morbidity

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years with craniopharyngiomas **I/C** which classification system (and therefore which radiological features) is most sensitive at predicting **O** the long-term risk of hypothalamo-pituitary dysfunction?	1. Craniopharyngioma/ or craniopharyngioma*.mp. 2. (classif* or stag* or grad*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 3. exp craniopharyngioma/ 4. exp classification/ 5. exp neoplasm staging/ 6. exp neoplasm grading/ 7. 1 and 2 8. 4 or 5 or 6 9. 3 and 8 10. 7 or 9 11. limit 10 to "all child (0 to 18 years)" 12. limit 11 to english language	325	207	11	9

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Yang et al., 2021(54)	Retrospective cohort	No	No	Yes – mixed cohort of adults and children (7/68 <14 years)	Yes – very unclear definitions of different independent and dependent variables	Yes – single centre	No	No	No
Park et al., 2013(50)	Retrospective cohort	No	No	No	No	Yes – single centre	Yes – highly significant association between post-operative grade and BMI at last follow-up	Yes – multivariate analysis accounted for all significant variables on univariate analysis	Yes – dose-response association between grade and BMI at last follow-up
Mallucci et al., 2012(55)	Retrospective cohort	No	No	No	Yes – relatively small cohort of 20 patients	Yes – single centre	No	No	No
Qi et al., 2012(51)	Retrospective cohort	No	Yes – hypothalamic tumours had lower incidences of endocrine dysfunction compared to other cohorts, no difference post-operatively	No	No	Yes – single centre	Yes – highly significant differences in post-operative BMI and hypothalamic status scores between groups	No	No

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Elliott et al., 2010(287)	Retrospective cohort	Yes – grading was mainly functional	No	No	No	Yes – single centre, single neurosurgeon	No	No	No
Trivin et al., 2009(52)	Retrospective cohort	No	No	No	Yes – relatively small cohort of 27 patients	Yes – single centre	No	Yes – radiologist blinded to outcomes	Yes – dose-response relationship between grade and BMI SDS/ fasting insulin/ ghrelin/ leptin
Puget et al., 2007(26)	Retrospective/ prospective cohort	No	No	No	No	Yes – single centre	Yes – highly significant associations between tumour grade and outcomes	No	Yes – dose-response relationship between grade and post-operative BMI SDS and QoL HUI2 score
De Vile et al., 1996(53)	Retrospective/ prospective cohort	Yes – grading was mainly functional	No	No	No	Yes – single centre	Yes – β>2 for hypothalamic dysfunction	No	No
Yasargil et al., 1990(336)	Retrospective cohort	Yes – no analysis of outcomes by grade	No	Yes – mixed cohort of adults and children (70/144 <16 years)	No	Yes – single centre, mainly by single neurosurgeon	No	No	No

Author(s)	Summary of findings					Quality
	No. of events in high grade craniopharyngiomas	No. of patients	No. of events in low grade craniopharyngiomas	No. of patients	Pooled effect	
Yang et al., 2021	<u>"Poor prognosis" (grades 3-4)</u> Multiple symptoms 25 Pituitary/ visual symptoms 7 Hypothalamic symptoms 25 Tumour size >2.5 cm 28 Large calcification 17 Solid tumour 9 "T" classification (hypothalamic) 30 Invasive tumour 20	 48 24 44 51 22 15 43 31	<u>"Poor prognosis" (grades 3-4)</u> "Single symptoms" 7 Tumour size <2.5 cm 4 No calcification 5 Cystic tumour 1 "Q" classification (largely intrasellar) 1 Loosely adhesive tumour 1	 20 17 25 10 7 9	Significant associations between presence of hypothalamo-pituitary symptoms, large tumour size, high degree of calcification, hypothalamic involvement, and tumour invasion, with poor prognosis	Very low
Park et al., 2013	BMI SDS 1.49 ± 1.08 Obesity (BMI >+1.65 SDS) 10	18	BMI SDS -0.14 ± 0.83 Obesity (BMI >+1.65 SDS) 2	19	Significant independent association of post-operative hypothalamic grade and BMI SDS at last follow-up	High
Mallucci et al., 2012	Progression 4 (all post-STR; 2 post-adjuvant radiotherapy, 2 treated with salvage radiotherapy)	13	Progression 0	2	No stratification of hypothalamo-pituitary dysfunction by grade but no change in BMI SDS, no new hypothalamic adipsia or hyperphagia	Very low
Qi et al., 2012	<u>Pre-operative endocrinology</u> GH deficiency 36 TSH deficiency 25 Delayed puberty 8 ACTH deficiency 12 Central DI 8 <u>Post-operative endocrinology</u> Median BMI 23.1 kg/m^2 (range 17.5-41.2) Hypothalamic status score 2.04 ± 0.97 Deaths 7 10-year OS 83% 10-year PFS 32%	 38 47 10 38 47 42 47	<u>Pre-operative endocrinology</u> GH deficiency 31 TSH deficiency 23 Delayed puberty 7 ACTH deficiency 17 Central DI 16 <u>Post-operative endocrinology</u> Median BMI 19.7 kg/m^2 (range 17.2-26.3) Hypothalamic status score 1.29 ± 0.57 Deaths 2 10-year OS 90% 10-year PFS 66%	 31 34 7 31 34 34 34	Hypothalamic tumours had significantly lower pre-operative prevalence of growth failure, ACTH deficiency, and central DI but significantly higher BMI and hypothalamic status score in hypothalamic group post-operatively	Very low
Elliott et al., 2010	N/A	N/A	N/A	N/A	High pre-operative Craniopharyngioma Clinical Status Scale scores independently predicted high post-operative scores in all domains	Very low

Author(s)	Summary of findings					Quality
	No. of events in high grade craniopharyngiomas	No. of patients	No. of events in low grade craniopharyngiomas	No. of patients	Pooled effect	
Trivin et al., 2009	Pre-operative (grade 2): BMI SDS 1.5 ± 1.3 HOMA-IR 3.65 ± 3.5 Fasting insulin 12.0 ± 11.8 mU/l Fasting glucose 5.1 ± 0.6 mmol/l Fasting ghrelin 1083 ± 222 g/l Fasting leptin 14.0 ± 9.8 µg/l Post-operative (grade 2) BMI SDS 4.0 ± 1.3 Change in weight SDS 2.5 ± 1.4 HOMA-IR 7.1 ± 9.0 Fasting insulin 47 ± 58 mU/l Fasting glucose 4.6 ± 0.7 mmol/l Fasting ghrelin 722 ± 126 ng/l Fasting leptin 61 ± 26 µg/l	12	Pre-operative (grade 0) BMI SDS 0.2 ± 2.0 HOMA-IR 1.31 ± 0.6 Fasting insulin 5.1 ± 2.4 mU/l Fasting glucose 4.4 ± 0.25 mmol/l Fasting ghrelin 2256 ± 331 ng/l Fasting leptin 5.6 ± 2.6 µg/l Post-operative (grade 0) BMI SDS 0.13 ± 1.3 Change in weight SDS 1.0 ± 1.2 Fasting insulin 10.1 ± 9.0 mU/l Fasting leptin 14.2 ± 14 µg/l	7	Significant associations between grade and pre-operative fasting glucose, insulin and ghrelin, and post-operative weight gain, fasting insulin and leptin	Low
Puget et al., 2007	Retrospective cohort BMI SDS Grade 2 2.8 ± 1.8 Grade 1 2.4 ± 1.6 Retrospective cohort HUI2 score Grade 2 0.51 ± 0.31 Grade 1 0.86 ± 0.11	 28 24 28 24	Retrospective cohort BMI SDS Grade 0 1 ± 1.6 Retrospective cohort HUI2 score Grade 0 0.92 ± 0.08	 14 4	Retrospective cohort: Post-operative BMI SDS significantly associated with pre- and post-operative grade (p=0.007 & 0.001 respectively) Post-operative HUI2 quality of life scores significantly associated with pre-and post-operative grade (p=0.001 and 0.003 respectively) No new hyperphagia, morbid obesity or behavioural dysfunction in prospective cohort	Moderate
De Vile et al., 1996	N/A	N/A	N/A	N/A	Post-operative morbidity score independently predicted by pre-operative hypothalamic dysfunction β 2.44 ± 0.88 Post-operative hypothalamic dysfunction associated with pre-operative hypothalamic disturbance	Very low
Yasargil et al., 1990	N/A	N/A	N/A	N/A	No analysis of outcomes by grade	Very low

Outcome 3.2.1.2.a Sensitivity and specificity of various conventional visual function tests for detecting visual dysfunction at diagnosis

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years with craniopharyngiomas I/C which of the following visual tests (in combination or alone) – visual acuity, visual field perimetry, visual evoked responses, electroretinogram O are most sensitive and specific for detecting visual dysfunction T at diagnosis?	1. craniopharyngioma*.mp. 2. limit 1 to "all child (0 to 18 years)" 3. (visual acuity or visual field or visual field perimetry or VER or ERG or visual evoked response* or electroretinogram*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 4. 2 and 3 5. Craniopharyngioma/ 6. limit 5 to "all child (0 to 18 years)" 7. Visual Acuity/ 8. Visual Fields/ 9. Visual Field Tests/ 10. Evoked Potentials, Visual/ 11. Electroretinography/ 12. 7 or 8 or 9 or 10 or 11 13. 6 and 12 14. "Sensitivity and Specificity"/ 15. 13 and 14 16. (sensitiv* or specific*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 17. 4 and 16 18. Vision Disorders/ 19. 13 and 18 20. (vision disorder* or visual disorder* or visual dysfunction* or vision dysfunction*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 21. 4 and 20 22. 17 or 19 or 21	56	34	11	3

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Drimtzias et al., 2014(57)	Retrospective cohort	Yes – only patients referred to joint ophthalmology – neuro-oncology clinic included, no control group	No	No	Yes – small cohort	No	No	No	No

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Suharwardy & Elston, 1997(56)	Retrospective cohort	Yes – no control group	No	Yes – mixed cohort of tumours (5/17 craniopharyngiomas)	Yes – very small cohort	Yes – only patients who had full ophthalmological assessment included	No	No	No
Wenzel et al., 1988(64)	Retrospective cohort	Yes – no control group	No	Yes – mixed cohort of tumour (16/68 craniopharyngiomas), unclear if pre- or post-diagnosis	No	Yes – unclear how patients selected	No	No	No

Author(s)	Summary of findings					Quality
	No. of positive tests in visually impaired group	No. of patients	Number of positive tests in non-visually impaired group	No. of patients	Pooled effect	
Drimtzias et al., 2014	Visual acuity reduction (logMAR/ preferential looking): 21 Visual field loss (Goldmann): 10 Optic atrophy: 12 Papilloedema: 6	40 eyes (20 patients) 14 patients 20 patients 20 patients	N/A	N/A	<u>Visual acuity:</u> Incidence 52.5% <u>Visual field:</u> Incidence 71% <u>Optic atrophy:</u> Incidence 60% <u>Papilloedema:</u> Incidence 30%	Very low
Suharwardy & Elston, 1997	Visual acuity reduction (Snellen): 5 Visual field loss (Goldmann): 5 Optic disc abnormalities: 5 Relative afferent pupillary defect: 5	5	N/A	N/A	Incidence 100%	Very low
Wenzel et al., 1988	N/A	N/A	N/A	N/A	Unclear re: numbers relating directly to craniopharyngioma but 61.8-91.2% had abnormal VEPs	Very low

Outcome 3.2.1.2.b Sensitivity and specificity of various OCT for detecting visual dysfunction at diagnosis

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years with craniopharyngiomas **I** how does OCT **C** compare to other traditional visual function testing techniques **O** in terms of sensitivity and specificity for detecting visual dysfunction **T** at diagnosis?	1. exp Craniopharyngioma/ or craniopharyngioma*.mp. 2. limit 1 to "all child (0 to 18 years)" 3. optical coherence tomography.mp. or exp Tomography, Optical Coherence/ 4. OCT.mp. 5. 3 or 4 6. 2 and 5	6	5	3	2

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Ju et al., 2019(69)	Retrospective cohort	Yes - mixed adult/ child cohort (unclear number of children)	No	Yes – mixed cohort of tumours (17/106) craniopharyngioma)	No	No	Yes	No	No
Bialer et al., 2013(68)	Retrospective cohort	Yes – only patients registered on ophthalmology databases included	No	Yes – unclear how many tests included in study were performed at diagnosis vs. post-treatment	Yes – small cohort	No	No	No	No

Author(s)	Summary of findings					Quality
	No. of abnormal OCTs in abnormal visual test group	No. of eyes	No. of abnormal OCTs in normal visual test group	No. of eyes	Pooled effect	
Ju et al., 2019	Retinal nerve fibre (RNFL) thickness: 75.3 µm Thin RNFL <69 µm: 15	38	RNFL thickness: 91.1 µm Thin RNFL <69 µm: 12	174	Optic tract oedema OR 5.7	Low
Bialer et al. 2013	RNFL thickness: 65 ± 22 µm	23	RNFL thickness: 85 ± 14 µm	24	Not calculable but significant correlations with visual acuity and visual field loss	Very low

Outcome 3.2.1.3.a & c: Sensitivity and specificity of routine endocrine testing at craniopharyngioma diagnosis

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years with craniopharyngiomas what is **O** the incidence of GH deficiency, precocious puberty, delayed puberty/ pubertal arrest, central hypothyroidism, ACTH deficiency and posterior pituitary dysfunction **T** at diagnosis?	1. craniopharyngioma.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 2. hypopituitarism.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 3. exp Craniopharyngioma/ 4. exp Hypopituitarism/ 5. endocrine dysfunction.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 6. endocrinopathy.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 7. 2 or 5 or 6 8. 1 and 7 9. 3 and 4 10. limit 8 to "all child (0 to 18 years)" 11. limit 9 to "all child (0 to 18 years)" 12. presentation.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 13. endocrine.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 14. 1 and 12 and 13 15. limit 14 to "all child (0 to 18 years)" 16. 10 or 11 or 15	304	50	33	0 (no direct evidence to support recommendation: Delphi consensus)

Outcome 3.2.1.3.b & c: Sensitivity and specificity of testing for ACTH deficiency

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years with hypothalamo-pituitary tumours **I** how do the following (in combination or alone): • 0900 cortisol • Standard synacthen test • Low-dose synacthen test • Physiological synacthen test • Glucagon stimulation test • CRH test **C** compare to the insulin tolerance test or metyrapone tests **O** in terms of sensitivity and specificity for detecting ACTH/ cortisol deficiency **T** at diagnosis?	1. (adrenocorticotrophic hormone deficiency or adrenocorticotropic hormone deficiency or ACTH deficiency).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 2. (secondary adrenal insufficiency or secondary adrenal deficiency).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 3. (central hypoadrenalism or central hypocortisolaemia or central hypocortisolemia or secondary hypoadrenalism).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 4. (corticotropin-releasing hormone deficiency or corticotrophin-releasing hormone deficiency or CRH deficiency).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 5. 1 or 2 or 3 or 4 6. (brain tumour or brain tumor or brain neoplasm).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 7. (diagnosis or test).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 8. (synacthen or synthetic adrenocorticotrophic hormone or synthetic adrenocorticotropic hormone or synthetic ACTH or cosyntropin or tetracosactide).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 9. (insulin tolerance test or glucagon stimulation test).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 10. 7 or 8 or 9 11. 5 and 6 and 10 12. exp Adrenal Insufficiency/ 13. exp Cosyntropin/ 14. exp Hypopituitarism/ 15. 12 or 13 or 14 16. exp Brain Neoplasms/ 17. exp Diagnosis/ 18. exp "Predictive Value of Tests"/ 19. (sensitivity and specificity).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 20. 17 or 18 or 19 21. 15 and 16 and 20 22. 11 or 13 or 21 23. limit 22 to (humans and "all child (0 to 18 years)")	540	17	13	5

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Cho et al., 2014(76)	Prospective case-control	No	No	Yes: adult patients with mixed causes for hypopituitarism (including non-tumour causes)	No	No	Yes	No	N/A
Kazlauskaite et al., 2008(77)	Meta-analysis of observational studies	No	No	Yes: mixed cohorts of adults and children, mixed causes for hypopituitarism (including non-tumour causes)	No	No	Yes	No	N/A
Maguire et al., 2008(79)	Prospective case-control	Yes: small control cohort, CRH test used as gold standard	Yes: very low cortisol cut-off for low-dose synacthen (peak 267 nmol/l)	Yes: mixed causes for hypopituitarism (including non-tumour causes)	No	No	Yes	No	N/A
Maghnie et al., 2005(78)	Prospective cohort	Yes: small cohort	No	Yes: mixed cohort of adults and children, mixed causes for hypopituitarism (none craniopharyngioma)	No	No	No	No	N/A
Gleeson et al., 2003(75)	Retrospective cohort	Yes: used clinical outcomes as gold standard	No	Yes: largely adult patients, mixed causes for hypopituitarism (4 craniopharyngioma)	No	No	Yes	No	N/A

Author(s)	Summary of findings					Quality
	No. of positive tests in ACTH deficiency group	No. of patients	Number of positive tests in non-ACTH deficient group	No. of patients	Pooled effect	
Cho et al. 2014	Low dose synacthen (1 µg): 69 Standard synacthen (250 µg): 64	83	Low dose synacthen (1 µg): 16 Standard synacthen (250 µg): 1	99	Low dose synacthen (1 µg): Sensitivity 83.1% (73.3-90.5) Specificity 83.8% (75.1-90.5) Standard synacthen (250 µg) : Sensitivity 77.1% (66.6-85.6) Specificity 99.0% (94.5-100.0)	Low
Kazlauskaite et al., 2008	N/A	N/A	N/A	N/A	Low dose synacthen (1 µg): AUC 0.94 (0.90-0.94) Standard synacthen (250 µg): AUC 0.82 (0.78-0.86) Morning cortisol (0800-1000h): AUC 0.79 (0.75-0.82)	Low
Maguire et al., 2008	N/A	N/A	N/A	N/A	Low-dose synacthen (0.5 µg/1.73 m^2): Sensitivity 83% Specificity 100% 0900h cortisol: Sensitivity 83% Specificity 75% (both compared to CRH)	Very low
Maghnie et al., 2005	Low dose synacthen (1 µg): 5 Standard synacthen (250 µg): 3 CRH test (1 µg/kg): 9	11	Low dose synacthen (1 µg): 0 Standard synacthen (250 µg): 0 CRH test (1 µg/kg): 3	5	Low dose synacthen (1 µg): Sensitivity 45% Specificity 100% Standard synacthen (250 µg): Sensitivity 27% Specificity 100% CRH test (1 µg/kg): Sensitivity 82% Specificity 40%	Very low
Gleeson et al., 2003	N/A	N/A	N/A	N/a	Standard synacthen (250 µg): Sensitivity 91% 0900h cortisol (<400 nmol/l) vs. SST: Sensitivity 91% Specificity 85%	Very low

Outcome 3.2.1.3.d Sensitivity and specificity of TRH testing for TRH/ TSH deficiency

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years with hypothalamo-pituitary tumours **I** how does a TRH stimulation test **C** compare to a random thyroid function test **O** in terms of sensitivity and specificity for detecting central hypothyroidism **T** at diagnosis?	1. (central hypothyroidism or secondary hypothyroidism or tertiary hypothyroidism).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 2. (thyroid-stimulating hormone deficiency or TSH deficiency or thyroid-stimulating hormone insufficiency or TSH insufficiency or thyrotropin deficiency or thyrotrophin deficiency or thryotropin insufficiency or thyrotrophin insufficiency).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 3. (thyrotropin-releasing hormone deficiency or thyrotrophin-releasing hormone deficiency or TRH deficiency or thyrotropin-releasing hormone insufficiency or thyrotrophin-releasing hormone insufficiency or TRH insufficiency).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 4. 1 or 2 or 3 5. (brain tumour or brain tumor or brain neoplasm).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 6. (diagnosis or test).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 7. (thyrotropin-releasing hormone test or thyrotrophin-releasing hormone test or TRH test).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 8. 6 or 7 9. 4 and 5 and 8 10. exp hypothyroidism/ or exp myxedema/ 11. exp Thyrotropin/ or exp Thyrotropin-Releasing Hormone/ 12. exp Hypopituitarism/ 13. 10 or 11 or 12 14. exp Brain Neoplasms/ 15. exp Diagnosis/ 16. exp "Predictive Value of Tests"/ 17. exp "Sensitivity and Specificity"/ 18. exp Thyroid Function Tests/ 19. 15 or 16 or 17 20. 13 and 14 and 18 and 19 21. 9 or 20 22. limit 21 to "all child (0 to 18 years)" 23. 7 or 21 24. limit 23 to "all child (0 to 18 years)" 25. 22 or 24	258	8	4	4

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Crofton et al., 2008(82)	Retrospective case control	Yes: retrospective study with only patients undergoing TRH testing selected, may have excluded more severe central hypothyroidism	No	Yes: mixed causes for hypopituitarism (9 with brain tumours)	No	No	No	Yes: multiple causes means that these could have increased effect size but no differences were found	N/A
Hartoft-Nielsen et al., 2004(81)	Prospective case control	No	No	Yes: mixed cohort of adults and children, mixed causes for hypopituitarism (including post-treatment, 29 brain tumours)	Yes: wide confidence intervals	No	No	Yes: multiple causes means that these could have increased effect size but no differences were found	N/A
Mehta et al., 2003(83)	Retrospective case control	Yes: retrospective study with only patients undergoing TRH testing selected, may have excluded more severe central hypothyroidism	No	Yes: all congenital hypopituitarism cases	No	No	No	Yes: multiple causes means that these could have increased effect size but no differences were found	N/A
Gruneiro-Papendieck et al., 1998(337)	?Retrospective case control	No	No	Yes: mixed causes (12 brain tumours)	No	No	No	No	N/A

Author(s)	Summary of findings					Quality
	No. of positive TRH tests in central hypothyroidism group	No. of patients	Number of positive TRH tests in non-central hypothyroidism group	No. of patients	Pooled effect	
Crofton et al., 2008	3	4	N/A (unclear if TRH performed whilst T_4 treatment started)	N/A	N/A Note no differences between hypothalamic and pituitary causes	Very low
Hartoft-Nielsen et al., 2004	N/A	N/A	N/A	N/A	N/A Note no differences in TRH responses between control group	Very low
Mehta et al., 2003	N/A	N/A	N/A	N/A	N/A Note no differences between hypothalamic and pituitary causes	Very low
Gruneiro-Papendieck et al., 1998	10	15	11	27	Sensitivity: 67% Specificity: 59%	Very low

Outcome 3.2.1.3.e: Sensitivity and specificity of testing for diabetes insipidus

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years with hypothalamo-pituitary tumours **I** how do the following (in combination or alone: • Paired early morning urine/ plasma osmolalities (urine: plasma <1) • Urine specific gravity <1.010 • Polyuria >5 ml/kg/hour • Absence of posterior pituitary bright spot on MRI • Plasma AVP • Urinary copeptin **C** compare to a water deprivation test **O** in terms of sensitivity and specificity for detecting diabetes insipidus **T** at diagnosis?	1. (diabetes insipidus or DI).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 2. (antidiuretic hormone deficiency or vasopressin deficiency or arginine-vasopressin deficiency or ADH deficiency or AVP deficiency).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 3. (posterior pituitary dysfunction or posterior pituitary deficit).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 4. 1 or 2 or 3 5. (brain tumour or brain tumor or brain neoplasm).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 6. (water deprivation test or paired osmolality or paired osmolalities or urinary copeptin or plasma vasopressin or plasma antidiuretic hormone or plasma arginine-vasopressin or plasma ADH or plasma AVP).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 7. 4 and 5 and 6 8. 4 and 6 9. exp diabetes insipidus/ or exp diabetes insipidus, neurogenic/ 10. exp Brain Neoplasms/ 11. exp "Predictive Value of Tests"/ 12. exp "Sensitivity and Specificity"/ 13. exp Diagnosis/ 14. 11 or 12 or 13 15. 9 and 10 and 14 16. 8 or 15 17. limit 16 to (humans and "all child (0 to 18 years)")	305	24	20	10

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Winzeler et al., 2019(103)	Prospective cohort	Yes: children only included as controls having undergone arginine stimulation for GH deficiency (part of mixed age cohort)	No	Yes: cases were adult patients only, diagnosis based on 2-hour arginine-stimulation test	No	No	Yes: high sensitivity and specificity	No	Yes: gradient between complete and partial central DI and primary polydipsia
Nigro et al., 2018(102)	Prospective cohort	Yes: only patients with severe hypernatraemia (Na >155 mmol/l) included	No	Yes: adult patients only	No	No	Yes: high sensitivity and specificity	No	No
Tull et al., 2018(104)	Prospective cohort	No	No	No	Yes: very small cohort of patients with diabetes insipidus/ primary polydipsia	No	No	No	Yes: gradient between complete and partial central DI and primary polydipsia
Fenske et al., 2018(101)	Prospective cohort	Yes: diabetes insipidus criteria not the same as in children	No	Yes: adult patients only, comparison used hypertonic saline test + copeptin (not used in children)	No	No	Yes: high sensitivity and specificity	No	Yes: gradient between complete and partial central DI and primary polydipsia
Timper et al., 2015(100)	Prospective cohort (multicentre)	No	No	Yes: adult patients only, unknown (?mixed) causes	No	No	Yes: high sensitivity and specificity	No	Yes: gradient between complete and partial central DI and primary polydipsia
De Fost et al., 2015(98)	Retrospective cohort	Yes: inconsistent testing methodology between patients	No	Yes: adult patients only, mixed causes for central DI (8 brain tumours)	Yes: for copeptin, only 10 patients tested	No	Yes: high sensitivity and specificity	No	N/A
Liu et al., 2013(88)	Retrospective cohort	Yes: only studied patients already diagnosed with central DI	No	Yes: mixed causes (26 brain tumours)	No	No	No	No	N/A

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Fenske et al., 2011(99)	Prospective case-control	No	No	Yes: adult patients only, mixed causes (16 brain tumours)	No	No	Yes: high sensitivity and specificity	No	Yes: dose-response gradient of plasma copeptin between complete and partial central DI and primary polydipsia
Shimura, 1993(97)	Prospective case-control	Yes: very small cohort, n=9 children with complete and partial central DI	No	No	Yes: very small cohort, although note confidence intervals not particularly wide; also unclear underlying causes for central DI	No	No	No	Yes: dose-response gradient of urinary AVP between partial and complete central DI
Maghnie et al., 1992(89)	?Prospective cohort	Yes: no controls	No	Yes: mixed causes for central DI (11 brain tumours), note also includes "dipsogenic DI" (i.e. primary polydipsia)	No	No	No	No	N/A

Author(s)	Summary of findings					Quality
	No. of positive tests in central DI group	No. of patients	Number of positive tests in non-central DI group	No. of patients	Pooled effect	
Winzeler et al., 2019	N/A	N/A	N/A	N/A	<u>Arginine-stimulated 1-hour plasma copeptin <3.8 pmol/l:</u> Sensitivity 93% Specificity 92%	Low
Nigro et al., 2018	Hypernatraemic plasma copeptin <4.4 pmol/l: 5	5	Hypernatraemic plasma copeptin >4.4 pmol/l: Not detailed	Not detailed	<u>Hypernatraemic plasma copeptin <4.4 pmol/l:</u> Sensitivity 100% Speciificity 99%	Very low
Tull et al., 2018	Water-deprived plasma copeptin ≤3.5 pmol/l: 6	8	Water-deprived plasma copeptin >3.5 pmol/l: 5	6	<u>Water-deprived plasma copeptin ≤3.5 pmol/l:</u> Sensitivity 75% Specificty 83.3%	Low

Author(s)	Summary of findings					Quality
	No. of positive tests in central DI group	No. of patients	Number of positive tests in non-central DI group	No. of patients	Pooled effect	
Fenske et al., 2018	Water deprived urine osmolality <300 mOsm/kg: 51 Water deprivation + basal copeptin <2.6 pmol/l or 8-hour copeptin/ plasma sodium ratio <0.02: 58	59 59	Water deprived urine osmolality >300 mOsm/kg: 57 Water deprivation + basal copeptin >2.6 pmol/l or 8-hour copeptin/ plasma sodium ratio >0.02: 4	82 80	Water-deprived urine osmolality <300 mOsm/kg Sensitivity 86.4% Specificity 69.5% Water deprivation + basal copeptin <2.6 pmol/l or 8-hour copeptin/ plasma sodium ration <0.02 Sensitivity 98.3% Specificity 5%	Low
Timper et al., 2015	N/A	N/A	N/A	N/A	Water-deprived plasma AVP <1.8 pg/ml: Sensitivity 83% Specificity 96% Water-deprived plasma copeptin <4.9 pmol/l: Sensitivity: 94% Specificity: 96%	Low
De Fost et al., 2015	Water-deprived urine osmolality <680 mOsm/kg: 13 Water-deprived plasma osmolality >300 mOsm/kg: 13 Water-deprived plasma copeptin <2.5 pmol/l: 3	13 13 3	Water-deprived urine osmolality <680 mOsm/kg: 27 Water-deprived plasma osmolality >300 mOsm/kg: 27 Water-deprived plasma copeptin <2.5 pmol/l: 1	27 27 7	Water-deprived urine osmolality <680 mOsm/kg or plasma osmolality >300 mOsm/kg: Sensitivity 100% Specificity 100% Water-deprived plasma copeptin <2.5 pmol/l: Sensitivity 100% Specificity 86%	Very low
Liu et al., 2013	Absent posterior pituitary bright spot: 59	62	N/A	N/A	Absent posterior pituitary bright spot: Sensitivity 95%	Very low
Fenske et al., 2011	N/A	N/A	N/A	N/A	Water-deprived plasma copeptin <5 pmol/l: Sensitivity 96% Specificity 81% Water-deprived plasma AVP <1 pmol/l: Sensitivity 52% Specificity 46%	Low
Shimura, 1993	Water-deprived urine osmolality <601 mOsm/kg: 30 Water-deprived urinary AVP <20.9 pg/ml: 30	30	Water-deprived urine osmolality <601 mOsm/kg: 1 Water-deprived urinary AVP <20.9 pg/ml: 1	56	Water-deprived urinary AVP <20.9 pg/ml: Sensitivity 100% Specificity 98%	Very low
Maghnie et al., 1992	Water deprivation test: 10 Baseline plasma AVP <0.5 pmol/l: 15 Absent posterior pituitary bright spot: 11	14 15 11	N/A	N/A	Water deprivation test: Sensitivity 71% Baseline plasma AVP <0.5 pmol/l: Sensitivity 100% Absent posterior pituitary bright spot: Sensitivity 100%	Very low

Outcome 3.2.1.3.f: The usefulness of questionnaires in detecting hypothalamic syndrome at diagnosis

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years with hypothalamo-pituitary tumours does **I** a questionnaire seeking features of the hypothalamic syndrome **C** compare to standard clinical assessment **O** increase the rate of diagnosis of hypothalamic dysfunction (BMI >2 SDS, appetite dysregulation, sleep-wake cycle disturbance, temperature dysregulation) **T** at diagnosis?	1. hypothalamic syndrome.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 2. hypothalamic obesity.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 3. 1 or 2 4. (brain tumour or brain tumor or brain neoplasm).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 5. questionnaire.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 6. clinical assessment.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 7. 5 or 6 8. 3 and 4 and 7 9. exp Appetite Regulation/ or exp Feeding Behavior/ 10. exp Body Temperature Regulation/ 11. exp Obesity/ or exp Obesity, Morbid/ or exp Pediatric Obesity/ 12. exp Sleep Disorders/ or exp "Disorders of Excessive Somnolence"/ 13. 9 or 10 or 11 or 12 14. exp Brain Neoplasms/ 15. exp Hypothalamic Neoplasms/ 16. 14 or 15 17. exp Questionnaires/ 18. 13 and 16 and 17	37	16	7	6

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Brimeyer et al., 2016(109)	Prospective cohort	Yes: No control group	No	Yes: Questionnaires administered in survivors and not at diagnosis, mixed cohort of tumours (36 "central")	Yes: Wide confidence intervals	No	No	No	N/A
Joustra et al., 2014(110)	Prospective case-control	No	No	Yes: Questionnaires administered in survivors and not at diagnosis, only survivors of adult-onset non-functioning pituitary macroadenomas included, "control group" is not appropriate for this PICO question specifically	No	No	No	No	N/A
Nolan et al., 2013(111)	Prospective case-control	No	No	Yes: Questionnaires administered in survivors and not at diagnosis, mixed cohort of tumours (18 hypothalamic), "control group" is not appropriate for this PICO question specifically	No	No	No	No	N/A

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Verberne et al., 2012(113)	Prospective case-control	Yes: Phone invitation would have biased response rates	No	Yes: Questionnaires administered in survivors and not at diagnosis, mixed cohort of tumours (3 craniopharyngioma, 1 pituitary adenoma, rest unclear location)	No	No	No	Yes: Control group were non-CNS malignancy patients, potentially would have reduced effect	N/A
Biermasz et al., 2011(108)	Prospective case-control	Yes: Small subcohorts	No	Yes: Questionnaires administered in survivors and not at diagnosis, only survivors of adult-onset non-functioning pituitary macroadenomas included, "control group" is not appropriate for this PICO question specifically	Yes: Small subcohorts, wide confidence intervals	No	No	No	N/A
Van der Klaauw et al., 2008(112)	Prospective case-control	No	No	Yes: Questionnaires administered in survivors and not at diagnosis, possibly only survivors of adult-onset craniopharyngiomas and non-functioning pituitary macroadenomas included, "control group" is not appropriate for this PICO question specifically	No	No	No	No	N/A

Author(s)	Summary of findings					Quality
	No. of abnormal features in questionnaire group	No. of patients	No. of abnormal features in non-questionnaire group	No. of patients	Pooled effect	
Brimeyer et al., 2016	Excessive daytime sleepiness: 19 Sleep-disordered breathing: 25 Night waking: 14 Sleepiness: 16	129 153 153 153	N/A	N/A	N/A	Very low
Joustra et al., 2014	Abnormal actigraphy results: N/A Abnormal daytime sleepiness/ reduced sleep quality scores: N/A	N/A N/A	N/A	N/A	N/A	Very low
Nolan et al., 2013	N/A	N/A	N/A	N/A	Delayed sleep onset: OR 2.7 (1.1-6.5) Pittsburgh Sleep Quality Index (PSQI) >10 OR 1.3 (0.6-2.9)	Very low
Verberne et al., 2012	Increased somnolence, difficulty maintaining sleep: N/A	31	N/A	N/A	N/A	Very low
Biermasz et al., 2011	Reduced sleep efficiency, shorter REM sleep time, increased sleep duration, increased awakenings, increased PSQI: N/A	17	N/A	N/A	N/A	Very low
Van der Klaauw et al., 2008	Epworth Sleepiness Scale (ESS) >10: 9 Sleep apnoea: 8	27	N/A	N/A	N/A	Very low

Outcome 3.2.1.5.a: Sensitivity and specificity of routine histological and cytological fluid examination for craniopharyngioma diagnosis

PICO questions	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years with craniopharyngiomas how frequently does **I** does histological diagnosis **C** compared to pre-surgical radiological diagnosis **O** correlate in terms of sensitivity and specificity?	1. exp Craniopharyngioma/ or craniopharyngioma*.mp. 2. limit 1 to "all child (0 to 18 years)" 3. (histological or histology).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 4. exp Histology, Comparative/ or exp Histology/ 5. 3 or 4 6. radiology.mp. or exp Radiology/ 7. radiological.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 8. 6 or 7 9. 2 and 5 and 8	17	9	2	0 (Delphi consensus)
P In children <19 years with craniopharyngiomas **I** how does cytological examination of cyst fluid (e.g. for cholesterol crystals) **C** compare to pre-surgical radiological diagnosis alone **O** in terms of sensitivity and specificity?	1. exp Craniopharyngioma/ or craniopharyngioma*.mp. 2. limit 1 to "all child (0 to 18 years)" 3. cytology.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 4. (cytology or cytological or cyst fluid).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 5. cholesterol crystal*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 6. 3 or 4 or 5 7. 2 and 6	39	27	6	0 (Delphi consensus)

Outcome 3.2.1.5.b: The routine use of Ki67/ MIB L1 labelling or CTNNB1 mutation analysis in predicting prognosis

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years with craniopharyngiomas **I** does histological examination for Ki67 index/ MIB1 L1/ CTNNB1 mutation analysis **O** predict overall and progression-free survival?	1. craniopharyngioma*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 2. (immunohistochemi* or histolog*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 3. (beta-catenin or Ki67 or MIB1 or MIB-1).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 4. 2 or 3 5. (survival or recurren* or progressi*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 6. outcome*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 7. 5 or 6 8. 1 and 4 and 7 9. exp Craniopharyngioma/ 10. exp Immunohistochemistry/ 11. exp Histology, Comparative/ or exp Histology/ 12. exp beta Catenin/ 13. exp Cell Proliferation/ or exp Ki-67 Antigen/ 14. 10 or 11 or 12 or 13 15. exp Survival/ or exp Survival Analysis/ or exp Survival Rate/ or exp Disease-Free Survival/ 16. exp Prognosis/ 17. exp Recurrence/ 18. exp Disease Progression/ 19. 15 or 16 or 17 or 18 20. 9 and 14 and 19 21. 8 or 20 22. limit 21 to "all child (0 to 18 years)"	192	53	27	17

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Li et al., 2015(117)	Prospective cohort	No	No	Yes: mixed cohort of adults and children (mean age 29 years), although aberrant CTNNB1 expression remained independent risk factor on age-adjusted multivariate analysis	Yes: wide confidence intervals	No	Yes	No	N/A
Ogawa et al., 2015(118)	Retrospective cohort	Yes: no attempts to correct for confounding factors by multivariate analysis	No	Yes: mixed cohort of adults and children (mean age 41 years), of which 65/98 (66%) were confirmed adamantinomatous craniopharyngioma	N/A: confidence intervals not reported	No	N/A	No	N/A
Gomes et al., 2015(115)	Prospective cohort	Yes: no attempts to correct for confounding factors by multivariate analysis	No	No: pure paediatric cohort	N/A: confidence intervals not reported	No	N/A	No	N/A
Gong et al., 2014(116)	Retrospective cohort	Yes: only tumours undergoing GTR were included, lack of controls, no attempts to correct for confounding factors by multivariate analysis	No	No: pure paediatric cohort	No: confidence intervals relatively narrow	No	Yes	No	N/A
Ebrahimi et al., 2013(338)	Retrospective cohort	Yes: lack of controls, no attempts to correct for confounding by multivariate analysis	No	Yes: mixed cohort of adults & children and adamantinomatous & papillary craniopharyngiomas	No	No	No	No	N/A

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Qi et al., 2012(119)	Prospective cohort	Yes: due to nature of staining, only tumours undergoing GTR were included, lack of controls	No	Yes: mixed cohort of adults and children (mean age 26 years), of which only 34 were confirmed adamantinomatous craniopharyngiomas	N/A: confidence intervals not reported	No	N/A	No	N/A
Xia et al., 2011(339)	Retrospective case-control	Yes: no multivariate analysis	No	No	Yes: small sample size	No	No	No	N/A
Campanini et al., 2010(340)	Prospective cohort	Yes: lack of controls, no statistical analysis	No	Yes: mixed cohort of adults and children, although all adamantinomatous craniopharyngiomas	Yes: very small sample size	No	No	No	N/A
Rodriguez et al., 2007(341)	Case series & literature review	Yes: small case series (n=3), only looked at malignant craniopharyngiomas, no comparison to controls	No	Yes: mixed series of 2 adults and 1 child	Yes: very small sample size	Yes: case series of selected malignant cases	No	No	N/A
Xu et al., 2007(342)	Prospective cohort	Yes: Small numbers, losses to follow-up	No	Yes: mixed adamantinomatous and papillary craniopharyngiomas	No	No	No	No	N/A
Agozzino et al. 2006(343)	Prospective case-control	Yes: only radically excised tumours	No	Yes: mixed cohort of adults and children	Yes: small sample size	No	No	No	N/A
Izumoto et al., 2005(344)	Retrospective case-control	Yes: excluded 13 patients	No	Yes: mixed cohort of adults and children	No	No	No	No	N/A
Losa et al., 2004(345)	Prospective cohort	Yes: 10 recurrent tumours, no multivariate analysis	No	Yes: mixed cohort of adults and children	Yes: small sample size	No	No	No	N/A
Lubansu et al., 2003(346)	?Retrospective cohort	Yes: no multivariate analysis	No	Yes: mixed cohort of adults and children	Yes: small sample size	No	No	No	N/A

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
LeFrance et al. 2003(347)	?Retrospective cohort	Yes: no multivariate analysis, same cohort as Lubansu et al. (2004)	No	Yes: mixed cohort of adults and children	Yes: small sample size	No	No	No	N/A
Raghavan et al., 2000(348)	Retrospective case-control	Yes: 11 recurrent tumours, no multivariate analysis	No	Yes: mixed cohort of adults and children	Yes: small sample size	No	No	No	N/A
Uchino et al., 2000(349)	Retrospective case series	Yes: very small sample size	No	No	Yes: small sample size	Yes: case series	No	No	N/A

Author(s)	Summary of findings					Quality
	Abnormal genetics/ immunohistochemistry events	No. of patients	Normal genetics/ immunohistochemistry events	No. of patients	Pooled effect	
Li et al., 2015	Aberrant membranous β-catenin: 7 progressions, 7 deaths	19	Normal membranous β-catenin: 2 progressions, 2 deaths	31	HR (overall survival) 11.21 (1.08-116.51)	Very low
Ogawa et al., 2015	High expression of GH receptor: number of events not reported	46	Normal expression of GH receptor: number of events not reported	52	N/A	Very low
Gomes et al., 2015	High expression of SMO and SUFU mRNA: number of events not reported	N/A	Normal expression of SMO and SUFU mRNA: number of events not reported	N/A	N/A	Very low
Gong et al., 2014	High expression of CXCL12: 9 High expression of CXCR4: 10	15 14	Low expression of CXCL12: 9 Low expression of CXCR4: 8	31 31	CXCL12: HR 3.57 (1.40-9.05) CXCR4: HR 4.39 (1.71-11.2)	Very low
Ebrahimi et al., 2013	Higher stromal osteonectin expression: number of events not reported	N/A	Lower stromal osteonectin expression: number of events not reported	N/A	N/A	Very low
Qi et al., 2012	High vimentin expression: 11 recurrences Low E-cadherin expression: 9 recurrences	13	Low vimentin expression: 2 recurrences High E-cadherin expression: 1 recurrence	29	N/A	Very low
Xia et al., 2011	Positive MMP9 expression: 15 recurrences Positive VEGF expression: 14 recurrences Disrupted COLIV expression: 14	25 25 26	Negative MMP9 expression: 1 recurrence Negative VEGF expression: 2 Intact COLIV expression: 2	15 15 14	N/A	Very low
Campanini et al., 2010	N/A	N/A	N/A	N/A	N/A	Very low
Rodriguez et al., 2007	N/A	N/A	N/A	N/A	N/A	Very low
Xu et al., 2007	Rate of MCM6 LI in recurrent tumours: 37.9%	N/A	Rate of MCM LI in non-recurrent tumours: 18%	N/A	N/A	Very low
Agozzino et al., 2006	Rate of various markers in recurrent tumours: MIB-1 L1 27.5% VEGF 70% Mean vascular density 9.9	N/A	Rate of various markers in non-recurrent tumours: MIB-1 L1 22.1% VEGF 40% Mean vascular density 9.3	N/A	N/A	Very low
Izumoto et al., 2005	Oestrogen and progesterone receptor positive: 1 (also high Ki67 index correlated with recurrence)	9	Oestrogen and progesterone receptor negative: 6	21	N/A	Very low
Losa et al., 2004	Ki67/ cyclin A do not predict recurrence	N/A	N/A	N/A	N/A	Very low

Author(s)	Summary of findings					Quality
	Abnormal genetics/ immunohistochemistry events	No. of patients	Normal genetics/ immunohistochemistry events	No. of patients	Pooled effect	
Lubansu et al., 2003	Cathepsin and retinoid acid receptor levels of expression associated with recurrence	N/A	N/A	N/A	N/A	Very low
LeFranc et al., 2003	Retinoic acid receptor levels of expression associated with recurrence	N/A	N/A	N/A	N/A	Very low
Raghavan et al., 2000	MIB-LI levels not significantly associated with recurrence	N/A	N/A	N/A	N/A	Very low
Uchino et al., 2000	GH receptor positive: 2	N/A	GH receptor negative: 0	N/A	N/A	Very low

Outcome 3.2.2.1.a: Management by specialist paediatric neurosurgeons

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years with craniopharyngiomas **I/C** does involvement of an experience paediatric neurosurgeon/ adult neurosurgeon with paediatric experience/ ENT surgeon performing a certain number of surgeries per year **O** improve overall and progression-free survival?	1. exp *Craniopharyngioma/ or craniopharyngioma*.mp. 2. limit 1 to "all child (0 to 18 years)" 3. surgery.mp. or exp *General Surgery/ 4. neurosurgery.mp. or exp *Neurosurgery/ 5. neurosurgeon.mp. or exp *Neurosurgeons/ 6. exp *Otolaryngology/ or ENT.mp. 7. ear nose throat.mp. 8. 3 or 4 or 5 or 6 or 7 9. 2 and 8	1549	38	8	5

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Van Lindert et al., 2010(124)	Prospective cohort	Yes – single centre, experience of single neurosurgeon	No	Yes – mixed cohort of adults and children, mixed cohort of tumours (7 craniopharyngioma)	Yes – small subcohort of craniopharyngiomas	Yes – single centre experience of single neurosurgeon	No	No	No
Locatelli et al., 2010(121)	Retrospective cohort	Yes – single centre, experience of a single ENT surgeon and single neurosurgeon	No	Yes – mixed cohort of tumours (7 craniopharyngiomas)	Yes – small subcohort of craniopharyngiomas	Yes – single centre experience	No	No	No
Klimo et al., 2009(120)	Retrospective cohort	Yes - two-centre but unclear how many different surgeons were operating	No	Yes – mixed cohort of tumours (3 craniopharyngiomas)	Yes – small subcohort of craniopharyngiomas	Unclear	No	No	No
Stamm et al., 2008(123)	Retrospective cohort	Yes – two-centre but unclear how many different surgeons were operating	No	Yes – mixed cohort of adults and children	Yes – very small cohort	Unclear	No	No	No
Sanford, 1994(122)	Retrospective cohort (conducted by multicentre national survey)	Yes – no multivariate analysis of various factors (different centres had different treatment strategies)	No	No	No	Yes – poor return rate of survey (11/58 centres)	Yes – large odds ratios	No	No

Author(s)	Summary of findings					Quality
	No. of events in centres with specialist neuro/ ENT surgeons	No. of patients	No. of events in centres without specialist neuro/ ENT surgeons	No. of patients	Pooled effect	
Van Lindert et al., 2010	Did not analyse survival as outcome	N/A	N/A	N/A	N/A	Very low
Locatelli et al., 2010	Did not analyse survival as outcome	N/A	N/A	N/A	N/A	Very low
Klimo et al., 2009	Did not analyse survival as outcome	N/A	N/A	N/A	N/A	Very low
Stamm et al., 2008	Did not analyse survival as outcome	N/A	N/A	N/A	N/A	Very low
Sanford 1994	"Poor outcome": 4 Death: 2	45	"Poor outcome": 12 Death: 2	23	"Poor outcome": OR 4.4 Death: OR 2.0	Very low

Outcome 3.2.2.2.b-c: Effectiveness of surgical resection/ cyst aspiration/ biopsy vs. conservative management

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years with craniopharyngiomas how effective are **I** the following procedures – complete resection, subtotal/ partial resection, cyst aspiration without resection, biopsy only **C** compared to conservative management **O** in increasing overall and progression-free survival?	1. exp *Craniopharyngioma/ or craniopharyngioma*.mp. 2. limit 1 to "all child (0 to 18 years)" 3. exp *Disease-Free Survival/ or exp *Survival/ or survival.mp. 4. 2 and 3 5. resection*.mp. 6. cyst aspiration*.mp. 7. biops*.mp. 8. biopsy.mp. or exp *Image-Guided Biopsy/ or exp *Biopsy/ 9. 5 or 6 or 7 or 8 10. 4 and 9	147	86	39	16

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Tan et al., 2018	Meta-analysis of cohort studies	No	No	Yes – for long-term endocrinopathies, indirect evidence over different treatment eras rather than head-to-head comparisons	Yes – aggregated rather than individual data analysed	No	No	No	No
Sterkenburg et al., 2015(34)	Prospective cohort	Yes – note no conservative management group, no multivariate analysis	No	No	No	No	No	Yes – patients from multicentre, multi-country HIT-ENDO registry	No
Lo et al., 2014(139)	Retrospective cohort	Yes – single centre	Yes – demonstrates GTR results in poorer PFS vs. STR + radiotherapy	Yes – mixed cohort of adults and children (46% <20 years)	Yes – wide confidence intervals	Yes – single centre	Yes – large hazard ratios	No	No
Iannalfi et al., 2013(127)	Systematic review of cohort studies	Yes – note study mainly directed towards studying the efficacy of radiotherapy, no meta-analysis performed	No	Yes – studies included mixed cohorts of adults and children	No	Yes – studies included only included trials involving radiotherapy	No	Yes – multiple cohort studies in different centres with different strategies/ techniques	No

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Clark et al. 2013(126)	Systematic review of cohort studies	Yes – no multivariate analysis performed, tumour grade/ location not determined	No	No	No	Yes – no control group (conservative management)	No	Yes – multiple cohort studies in different centres with different strategies/ techniques	No
Zacharia et al., 2012(7)	Retrospective cohort	Yes – tumour grade/ location not included in multivariate analysis (only size included)	Yes – demonstrates GTR results in equivalent OS to observation or biopsy, whilst STR increases OS	Yes – mixed cohort of adults and children (31.2% <19 years), mixed cohort of craniopharyngioma histologies (29.7% adamantinomatous)	No	No	Yes – HR <0.5 for STR	Yes – multivariate analysis of a national registry of cases from multiple centres	No
Schoenfeld et al., 2012(130)	Retrospective cohort	Yes – single centre, no multivariate analysis, tumour grade/ location not determined	No	Yes – mixed cohort of adults and children (median age 30 (IQR 11-52) years), mixed cohort of craniopharyngioma histologies (65% adamantinomatous)	Yes – some confidence intervals very wide	Yes – single centre only	Yes – hazard ratios for STR vs. STR + radiotherapy >2, GTR vs. STR <0.5	No	No
Zhao et al., 2012(137)	Retrospective cohort	Yes – single centre	No	Yes – mixed cohort of adults and children (median age 27 (range 21 months – 68 years), unclear proportion of different craniopharyngioma histologies, some patients with recurrent tumours	Yes – very wide confidence intervals	Yes – single centre only, all having undergone surgery	Yes – hazard ratios for STR vs. GTR >2	No	No

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Elliott & Wisoff, 2010(131)	Retrospective cohort	Yes – single centre, tumour grade/ location not included in multivariate analysis (only size included)	No	Yes – some recurrent tumours with previous surgery +/- radiotherapy	Yes – very wide confidence intervals, small cohort	Yes – single centre only, all having undergone surgery, and all tumours "giant" (>5 cm diameter)	No	No	No
Muller et al., 2010(134)	Prospective cohort	Yes – no effort made to grade tumours	No	No	No	No	Yes – GTR vs. STR HR <0.5	Yes – multicentre, multi-country study with multivariate analysis	No
Yang et al., 2010(136)	Systematic review of cohort studies	Yes – no multivariate analysis, tumour grade/ location/ size not determined	No	Yes – mixed cohort of adults and children, unclear proportion of different histologies	No (but no confidence intervals reported)	No	No (but hazard ratios not reported)	Yes – multiple cohort studies in different centres with different strategies/ techniques	No
Gupta et al., 2006(132)	Retrospective cohort	Yes – no multivariate analysis, tumour grade/ location not determined (only size included)	No	No	No (but no confidence intervals reported)	No	No (but hazard ratios not reported)	No	No
Ersahin et al., 2005(140)	Retrospective cohort	Yes – no multivariate analysis, unclear definition of GTR vs. STR vs. near total resection vs. partial resection	No	No	No (but no confidence intervals reported)	Yes – unclear how cases selected (?only surgical cases chosen)	No (but no ratios reported directly)	Yes – multicentre study in different centres with different treatment strategies	No
Tomita & Bowman, 2005(135)	Retrospective cohort	Yes – single centre experience of single neurosurgeon with overarching aim for GTR, no multivariate analysis	No	No	No (but no confidence intervals reported)	Yes – single centre experience of single neurosurgeon, relatively small cohort	No (but not ratios reported directly)	No	No
Fisher et al., 1998(62)	Retrospective cohort	Yes – single centre, unclear if multivariate analysis performed	No	No	Yes – small cohort (no confidence intervals reported)	Yes – single centre	No	No	No

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Zuccaro et al., 1996)(138)	Retrospective cohort	Yes – single centre with overarching aim for GTR, no multivariate analysis performed	No	No	Yes – relatively small cohort	Yes – single centre	No	No	No

Author(s)	Summary of findings					Quality
	No. of events in intervention group	No. of patients	No. of events in control group	No. of patients	Pooled effect	
Tan et al., 2018	Recurrence rate GTR 11	 45	Recurrence rate Incomplete resection + radiotherapy 22	 76	 Recurrence rate GTR vs. incomplete resection + radiotherapy OR 0.8 (calculated)	Low
Sterkenburg et al., 2015	20-year OS: GTR 89(79-99)% Hypothalamic involvement 84(76-92)% 20-year PFS: GTR 65(19-78)% Hypothalamic involvement 56(42-70)%	 91 132 65 85	20-year OS: STR 87(79-95)% No hypothalamic involvement 95(87-100)% STR 48(49-81)% No hypothalamic involvement 62(44-80)%	 132 82 87 53	Univariate OS: GTR vs. STR: p=NS Hypothalamic vs. non-hypothalamic involvement: p=0.006 Univariate PFS: GTR vs. STR: p=NS Hypothalamic vs. non-hypothalamic involvement: p=NS	Low
Lo et al., 2014	10-year PFS: GTR 29% STR 26% Cyst drainage 0% STR + radiotherapy 82% Cyst drainage + radiotherapy 83% 10-year OS: Breakdown by primary treatment strategy not stated	 18 35 14 48 6	N/A	N/A	Multivariate PFS: GTR vs. STR + radiotherapy HR 23.1(5.2-103.5) Cyst aspiration + radiotherapy vs. STR + radiotherapy HR 1.4(0.2-11.7) Cyst aspiration vs. STR + radiotherapy HR 26.8(6.7-106.8) No significant differences in disease-specific OS in all multivariate analyses	Very low
Iannalfi et al., 2013	N/A	N/A	N/A	N/A	No meta-analysis performed	Very low
Clark et al., 2013	Recurrence rates: GTR 51 STR 51 STR + radiotherapy 27 Biopsy + chemotherapy 9 5-year PFS: GTR 77% STR + radiotherapy 73% STR 43%	 135 79 54 22	N/A	N/A	Univariate PFS: STR vs. GTR HR 1.4(1.1-1.8)	Moderate

Author(s)	Summary of findings					Quality
	No. of events in intervention group	No. of patients	No. of events in control group	No. of patients	Pooled effect	
Zacharia et al., 2012	3-year OS: GTR 82.6% STR 92.5%	 216 246	3-year OS: Observation/ biopsy 82.3%	 176	Multivariate OS: GTR vs. observation/ biopsy HR 1.22 (0.71-2.08) STR vs. observation/ biopsy HR 0.45 (0.23-0.85)	Very low
Schoenfeld et al., 2012	2-year PFS: GTR 75% STR 36% STR + radiotherapy 73% 10-year OS: GTR 96% STR 81% STR + radiotherapy 96%	 33 37 46 33 37 46	N/A	N/A	Univariate PFS: GTR vs. STR + radiotherapy HR 1.24(0.62-2.49) STR vs. STR + radiotherapy HR 4.15(2.26-7.61) GTR vs. STR HR 0.30(0.16-0.56) Univariate OS: GTR vs. STR + radiotherapy HR 0.66(0.06-7.40) STR vs. STR + radiotherapy HR 4.88(1.00-23.74) GTR vs. STR HR 0.14(0.16-1.14)	Very low
Zhao et al., 2012	Progression/ recurrence: GTR 7 GTR + radiotherapy 3 STR 13 STR + radiotherapy 32 Deaths: GTR 7 STR 6 STR + radiotherapy 6	 69 37 13 32 106 12 32	N/A	N/A	Multivariate OS: STR vs. GTR 12.66(1.96-81.67) No difference in recurrence rate GTR vs. GTR + radiotherapy Significant differences in recurrence rate for GTR +/- radiotherapy > STR + radiotherapy, STR > STR + radiotherapy	Very low
Elliott & Wisoff, 2010	Disease control: GTR 95% STR +/- radiotherapy 50%	 20 6	N/A	N/A	Disease control GTR vs. STR $p<0.05$	Very low
Muller et al., 2010	Progression/ recurrence/ death: GTR 36% STR 69%	 47 64	N/A	N/A	Multivariate event-free survival GTR vs. STR HR 0.20(0.10-0.39)	Moderate
Yang et al., 2010	5-year PFS: GTR 67% STR 34% STR + radiotherapy 69% 10-year OS: GTR 98% STR 93% STR + radiotherapy 95%	 256 101 85 256 101 85	N/A	N/A	PFS significantly higher in GTR vs. STR but not STR + radiotherapy No differences in OS	Very low
Gupta et al., 2006	Recurrence: GTR 2 GTR + radiotherapy 0 STR 4 STR + radiotherapy 9	 16 3 17 36	N/A	N/A	Recurrence rate GTR vs. STR OR 0.64 (calculated)	Very low

Author(s)	Summary of findings					Quality
	No. of events in intervention group	No. of patients	No. of events in control group	No. of patients	Pooled effect	
Ersahin et al., 2005	Recurrence: GTR 2 STR 12 Deaths: All deaths occurred in patients undergoing GTR or STR (vs. partial resections)	 37 43	N/A	N/A	Extent of resection significantly related to long-term neurodisability (Glasgow Outcome Scale – but unclear direction of effect) Recurrence rate GTR vs. STR OR 0.19 (calculated)	Very low
Tomita & Bowman, 2005	Recurrence: GTR 9 STR 12 STR + radiotherapy 3 10-year recurrence-free survival: GTR 70% STR 9% STR + radiotherapy 36%	 33 13 8	N/A	N/A	Recurrence rate GTR vs. STR OR 0.38 (calculated)	Very low
Fisher et al., 1998	N/A	N/A	N/A	N/A	PFS not associated with extent of resection	Very low
Zuccaro et al., 1996	Recurrences: GTR 0 STR 15 Deaths: GTR 0 STR 6 Cyst aspiration + biopsy 0	 13 28 13 28 7	N/A	N/A	No statistical analyses performed	Very low

Outcome 3.2.2.2.d: Management of hydrocephalus

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years with craniopharyngiomas and hydrocephalus what is the efficacy of **I** the following procedures – external ventricular drain insertion, transventricular/ transsphenoidal endoscopic cyst drainage, reservoir insertion **C** compared to conservative management **O** in relieving intracranial pressure symptoms?	1. exp *Craniopharyngioma/ or Craniopharyngioma*.mp. 2. limit 1 to "all child (0 to 18 years)" 3. (external ventricular drain* or EVD).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 4. ommaya.mp. 5. (transventricular or transsphenoidal).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 6. endoscopic.mp. 7. 5 and 6 8. 3 or 4 or 7 9. exp *Hydrocephalus/ or hydrocephalus.mp. 10. 2 and 9 11. 8 and 10	16	10	4	3

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Khan et al., 2013(147)	Retrospective cohort	Yes – single centre, unclear if Ommaya reservoir insertion (as a significant protective factor against headache) was in the presence of hydrocephalus, only included Ommaya reservoir and ventriculoperitoneal shunts as techniques	No	No	No	Yes – single centre	No	No	No
Kim et al., 2013(148)	Retrospective cohort	Yes – primary aim of study was to look at the feasibility of neuroendoscopic biopsy in children	No	Yes – mixed cohort of tumours, only 1 craniopharyngioma, 17 with hydrocephalus	Yes – very small cohort	Yes – single centre	No	No	No

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Tirakotai et al., 2007(149)	Retrospective cohort	Yes – primary aim of study was to look at the feasibility of neuroendoscopic procedures	No	Yes – mixed cohort of adults and children (mean age 43.8 years), mixed cohort of tumours (7 craniopharyngiomas), 20 with hydrocephalus	Yes – very small cohort	Yes – single centre	No	No	No

Author(s)	Summary of findings					Quality
	No. of interventions in hydrocephalus group	No. of patients	No. of interventions in non-hydrocephalus group	No. of patients	Pooled effect	
Khan et al., 2013	N/A	N/A	N/A	N/A	Ommaya reservoir and headache frequency: multivariate OR 0.44 (0.18-1.12)	Very low
Kim et al., 2013	8 (3 shunts, 2 septostomies, 3 third ventriculostomies)	17	N/A	N/A	All patients needing decompression procedures had resolved hydrocephalus post-procedure	Very low
Tirakotai et al., 2007	20 (19 third ventriculostomies, 1 stent)	20	N/A	N/A	All patients needing decompression procedures had resolved hydrocephalus post-procedure	Very low

Outcome 3.2.2.2.e: Management of cystic craniopharyngiomas with hydrocephalus

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years with cystic craniopharyngiomas and hydrocephalus how effective are **I** the following procedures – transventricular/ transsphenoidal endoscopic cyst aspiration, reservoir insertion **C** compared to conservative management **O** in reducing the need for permanent ventriculoperitoneal shunting/ ventricular drainage?	1. exp *Craniopharyngioma/ or craniopharyngioma*.mp. 2. limit 1 to "all child (0 to 18 years)" 3. exp *Hydrocephalus/ or hydrocephalus.mp. 4. 2 and 3 5. (Ventriculoperitoneal shunt* or V-P shunt* or VP shunt*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 6. exp *Cerebrospinal Fluid Shunts/ or Ventricular drain*.mp. 7. exp *Ventriculoperitoneal Shunt/ 8. (transventricular or transsphenoidal).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 9. ommaya.mp. 10. 5 or 6 or 7 or 8 or 9 11. 4 and 10	48	19	9	3 (no clear agreement therefore Delphi consensus)

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Tirakotai et al., 2007(149)	Retrospective cohort	Yes – primary aim of study was to look at the feasibility of neuroendoscopic procedures,	No	Yes – mixed cohort of adults and children (mean age 43.8 years), mixed cohort of tumours (7 craniopharyngiomas), 20 with hydrocephalus, 15 cystic	Yes – very small cohort	Yes – single centre	No	No	No
Cinalli et al., 2006(150)	Case series	Yes – single centre case series	No	Yes - cohort included adult patients, unclear how many had hydrocephalus	Yes – 3 cases described only, only 2 cystic	Yes – single centre case series	No	No	No
Nicolato et al., 2004(151)	Case series	Yes – single centre case series, mixed treatment modalities including intracavitary brachytherapy and gamma knife radiosurgery	No	Yes – cohort included adult patients, 3 had hydrocephalus	Yes – case series	Yes – single centre case series	No	No	No

Author(s)	Summary of findings					Quality
	No. of interventions in hydrocephalus group	No. of patients	No. of interventions in non-hydrocephalus group	No. of patients	Pooled effect	
Tirakotai et al., 2007	20 (19 third ventriculostomies, 1 stent – unclear which tumours were cystic)	20	N/A	N/A	All patients needing decompression procedures had resolved hydrocephalus post-procedure	Very low
Cinalli et al., 2006	N/A	N/A	N/A	N/A	One patient had cystic decompression leading to relief of hydrocephalus	Very low
Nicolato et al., 2004	3 (all Ommaya reservoir)	3	N/A	N/A	All patients with hydrocephalus resolved immediately post-reservoir insertion	Very low

Outcome 3.2.2.2.f-g: Management of cystic craniopharyngiomas

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years with cystic craniopharyngiomas how effective are **I** the following procedures – transventricular/ transcranial/ transsphenoidal endoscopic cyst aspiration, reservoir insertion **C** compared to conservative management **O** in reducing maximum cyst diameter or reducing cyst relapse?	1. exp *Craniopharyngioma/ or craniopharyngioma*.mp. 2. limit 1 to "all child (0 to 18 years)" 3. transsphenoidal.mp. or exp *Endoscopy/ 4. transventricular.mp. 5. ommaya.mp. 6. cyst.mp. or exp *Cysts/ 7. cyst*.mp. 8. 3 or 4 or 5 9. 6 or 7 10. 2 and 8 and 9	128	42	16	11

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Frio et al., 2019(161)	Case series	Yes – single centre, no comparison group	No	Yes – adult cohort	Yes – case series, unclear definition of outcomes	Yes – single centre experience	No	No	No
Moussa et al., 2013(153)	Retrospective cohort	Yes – single centre, no comparison group	No	Yes – mixed cohort of adults and children (69% <16 years)	Yes – relatively small cohort	Yes – single centre experience	No	No	No
Gangemi et al., 2009(152)	Case report	Yes – single case	No	No	Yes – single case	Yes – single case	No	No	No
Cinalli et al., 2006(150)	Case series	Yes – single centre case series	No	Yes - cohort included adult patients, only 2 cystic	Yes – 3 cases described only, only 2 cystic	Yes – single centre case series	No	No	No
Delitala et al., 2004(154)	Case series	Yes – single centre case series	No	Yes – mixed cohort of adults and children (mean 50.1 years), 3 were relapsed craniopharyngiomas	Yes – 7 cases only	Yes – single centre case series	No	No	No
Locatelli et al., 2004(155)	Case series	Yes – single centre case series	No	Yes – all cases were relapsed craniopharyngiomas which had had previous resections	Yes – 5 cases only	Yes – single centre case series	No	No	No
Reda et al., 2002(156)	Case series	Yes – single centre case series	No	Yes – only one case of relapsed craniopharyngioma, cyst aspiration with radiosurgery	Yes – 2 cases presented only	Yes – single centre case series	No	No	No

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Joki et al., 2002(158)	Case report	Yes – single case	No	Yes – relapsed craniopharyngioma post-resection and cyst aspiration, Ommaya inserted then radiosurgery	Yes – single case	Yes – single case	No	No	No
Vitaz et al., 2001(160)	Case series	Yes – single centre case series	No	Yes – both relapsed craniopharyngiomas	Yes – 2 cases presented only	Yes – single centre case series	No	No	No
Nakamizo et al., 2001(159)	Case report	Yes – single case	No	No	Yes – single case	Yes – single case	No	No	No
Gutin et al., 1980(157)	Case series	Yes – single centre case series	No	Yes – mixed cohort of adults and children (2 <18 years), mixed cohort of primary and relapsed craniopharyngiomas	Yes – 4 cases presented only	Yes – single centre case series	No	No	No

Author(s)	Summary of findings					Quality
	No. of events in cyst aspiration/ Ommaya reservoir group	No. of patients	No. of events in conservatively managed group	No. of patients	Pooled effect	
Frio et al. ,2019	Tumour control: 73% Visual acuity improvement: 71% Visual field improvement: 88% Headache improvement: 100% Cognitive/ behavioural improvement: 44% Hypopituitarism improvement: 0%	11	N/A	N/A	N/A	Very low
Moussa et al., 2013	Reaccumulation: 14 (4 needed bleomycin)	52 Ommaya reservoir	N/A	N/A	N/A	Very low
Gangemi et al., 2013	N/A	N/A	N/A	N/A	Cystic aspiration was followed by GTR 1 week after	Very low
Cinalli et al., 2006	Reaccumulation: 0	2	N/A	N/A	One cystic aspiration led to control of hydrocephalus, followed by GTR	Very low
Delitala et al., 2004	Failure: 1 Relapse/ reaccumulation: 2	7 cyst-ventricular shunt	N/A	N/A	N/A	Very low
Locatelli et al., 2004	Relapse: 1	1 cyst marsupialisation 3 stent insertions 1 cyst-ventricular shunt	N/A	N/A	N/A	Very low
Reda et al., 2002	Relapse: 0	1	N/A	N/A	N/A	Very low
Joki et al., 2002	N/A	N/A	N/A	N/A	Ommaya reservoir insertion was followed by radiosurgery after	Very low

Author(s)	Summary of findings					Quality
	No. of events in cyst aspiration/ Ommaya reservoir group	No. of patients	No. of events in conservatively managed group	No. of patients	Pooled effect	
Vitaz et al., 2001	N/A	N/A	N/A	N/A	Both patients showed 40% & 85% reduction in cyst volume prior to ^{32}P instillation	Very low
Nakamizo et al., 2001	N/A	N/A	N/A	N/A	N/A	Very low
Gutin et al., 1980	Reaccumulation: 4	4 Ommaya reservoir	N/A	N/A	N/A	Very low

Outcome 3.2.2.2.h: The role of high-field intraoperative MRI

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years with craniopharyngiomas undergoing surgical resection does **I** the use of intraoperative MRI **C** compared to no intraoperative MRI **O** increase the incidence of successful GTR/STR, reduce the frequency of complications or of hypothalamo-pituitary dysfunction?	1. exp *Craniopharyngioma/ or craniopharyngioma*.mp. 2. limit 1 to "all child (0 to 18 years)" 3. magnetic resonance imaging.mp. or exp *Magnetic Resonance Imaging/ 4. MRI.mp. 5. intraoperative.mp. or exp *Monitoring, Intraoperative/ 6. 3 or 4 7. 2 and 5 and 6	37	22	7	6

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Hofmann et al., 2011(162)	Prospective cohort	Yes – no control group	No	Yes – mixed cohort of adults and children (mean age 31 years)	Yes – small cohort	Yes – single centre, note only included complex tumours >1cm with extension into >1 cranial fossa/ ventricles or large cystic/ calcified components	No	No	No
Samdani et al., 2005(166)	Retrospective cohort	Yes – no control group	No	Yes – mixed cohort of tumours (3/20 craniopharyngiomas)	Yes – small cohort	Yes – single centre	No	No	No
Nimsky et al., 2004(164)	Retrospective cohort	Yes – no control group	No	Yes – mixed cohort of adults and children (mean 46.1 years), mixed tumour types (11/200 craniopharyngiomas)	No	Yes – single centre	No	No	No
Nimsky et al., 2003(163)	Retrospective cohort	Yes – no control group	No	Yes – mixed cohort of adults and children (9/20 <19 years)	Yes – small cohort	Yes – single centre	No	No	No
Vitaz et al., 2001(160)	Case series	Yes – single centre case series	No	Yes – both relapsed cases	Yes – 2 cases reported	Yes – single centre case series	No	No	No

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Lam et al., 2001(165)	Case series	Yes – single centre case series	No	Yes – mixed cohort of tumours (1 cystic craniopharyngioma)	Yes – 9 cases reported	Yes – single centre case series	No	No	No

Author(s)	Summary of findings					Quality
	No. of events in intraoperative MRI group	No. of patients	No. of events in non-intraoperative MRI group	No. of patients	Pooled effect	
Hofmann et al., 2011	Intended GTR and successful GTR before MRI: 14 Intended STR and successful STR before MRI: 1 Intended GTR and successful GTR after MRI: 4 Intended STR and successful STR after MRI: 1	25	N/A	N/A	Increased rate of GTR by 16%	Very low
Samdani et al., 2005	Extension of resection post-MRI: 4	20	N/A	N/A	N/A	Very low
Nimsky et al., 2004	Intended GTR with extension of resection post-MRI: 26/65 Intended STR with extension of resection post-MRI: 17/46	139 pituitary adenomas/ gliomas/ craniopharyngiomas	N/A	N/A	Increased rate of GTR by 31.3% Increased extent of STR by 14.9% Increased success rate of cystic craniopharyngioma puncture in 2 patients	Very low
Nimsky et al., 2003	Intended GTR and successful GTR before MRI: 14 Intended GTR and successful GTR after MRI: 2 Recurrence post-GTR: 3	16	N/A	N/A	No additional morbidity from intraoperative MRI	Very low
Vitaz et al., 2001	Reduction in cyst size by 85% and 40% respectively	2	N/A	N/A	N/A	Very low
Lam et al., 2001	Intended GTR and successful GTR before MRI: 4 Intended GTR and successful GTR after MRI: 3 Intended GTR and successful STR after MRI: 2 1 craniopharyngioma cyst completely resolved	7	N/A	N/A	N/A	Very low

Outcome 3.2.2.2.a: The use of perioperative dexamethasone

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years with craniopharyngiomas undergoing transcranial and transsphenoidal surgical procedures does **I** the use of perioperative dexamethasone **C** compared to no perioperative dexamethasone **O** have an effect on overall survival, the likelihood of complete surgical resection and reducing the frequency of surgical complications and perioperative mortality?	1. dexamethasone.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 2. (preoperative or perioperative).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 3. (neurosurgery or neurosurgical or surgery or surgical).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 4. (brain tumour or brain tumor or brain neoplasm).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 5. 2 or 3 6. 1 and 4 and 5 7. exp Dexamethasone Isonicotinate/ or exp Dexamethasone/ 8. exp Preoperative Period/ or exp Preoperative Care/ 9. exp Perioperative Nursing/ or exp Perioperative Care/ or exp Perioperative Period/ 10. 8 or 9 11. exp Brain Neoplasms/ 12. exp Neurosurgery/ 13. 8 or 9 or 12 14. 7 and 11 and 13 15. 6 or 14	69	11	7	0

Outcome 3.2.2.2.b: The use of perioperative hydrocortisone

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years with craniopharyngiomas undergoing surgical procedures without perioperative dexamethasone does **I** the routine use of perioperative hydrocortisone in doses of 2mg/kg IV then 4-hourly thereafter, 2mg/kg IV then 6-8-hourly thereafter continuous IV infusion to achieve concentrations of 1000 nmol/l **C** compared to no perioperative hydrocortisone **O** increase overall survival, reduce the frequency of perioperative hypoadrenal crises and perioperative mortality?	1. hydrocortisone.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 2. (preoperative or perioperative).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 3. (neurosurgery or neurosurgical or surgery or surgical).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 4. (brain tumour or brain tumor or brain neoplasm).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 5. 2 or 3 6. 1 and 4 and 5 7. exp Hydrocortisone/ 8. exp Preoperative Period/ or exp Preoperative Care/ 9. exp Perioperative Nursing/ or exp Perioperative Care/ or exp Perioperative Period/ 10. exp Brain Neoplasms/ 11. exp Neurosurgery/ 12. 8 or 9 or 11 13. 7 and 10 and 12 14. 6 or 13	85	8	7	2

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
De Tommasi et al., 2012(350)	Case series	Yes – only transsphenoidal patients included, no control group	No	Yes – adult patients with pituitary macroadenomas only	Yes – 9 patients	Yes – single centre with predetermined protocols	No	No	No
Auchus et al., 1997(172)	Prospective cohort	Yes – only transsphenoidal patients included, no control group	No	Yes – adult patients, none with craniopharyngioma	Yes – relatively small cohort	Yes – single centre with predetermined protocol	No	No	No

Author(s)	Summary of findings					Quality
	No. of events in perioperative hydrocortisone group	No. of patients	No. of events in non-perioperative hydrocortisone group	No. of patients	Pooled effect	
De Tommasi et al., 2012	1	1	0	8	Only one patient with fatigue and postoperative mean serum cortisol of <500 nmol/l treated	Very low

Author(s)	Summary of findings					Quality
	No. of events in perioperative hydrocortisone group	No. of patients	No. of events in non-perioperative hydrocortisone group	No. of patients	Pooled effect	
Auchus et al., 1997`	Preoperatively normal HPA: 1 Preoperatively abnormal HPA: 3	17 6			48h postoperative 24h post-hydrocortisone) morning cortisol >270 nmol/l: Sensitivity 94% Specificity 100% (preop normal HPA) Sensitivity 67% Specificity 67% (preop abnormal HPA) 48h postoperative 24h post-hydrocortisone) morning cortisol <60 nmol/l: Sensitivity 100% Specificity 50% (preop normal HPA) Specificity 100% (preop abnormal HPA)	

Outcome 3.2.2.2.c: Perioperative testing for central diabetes insipidus

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years with craniopharyngiomas undergoing surgical procedures **I** how do the following (in combination or alone): • Paired early morning urine/ plasma osmolalities (urine: plasma <1) • Urine specific gravity <1.010 • Polyuria >5 ml/kg/hour • Plasma AVP • Urinary/ plasma copeptin **C** compared to a water deprivation test **O** in terms of sensitivity and specificity for detecting diabetes insipidus **T** in the postoperative period?	1. (diabetes insipidus or antidiuretic hormone deficiency or vasopressin deficiency or arginine-vasopressin deficiency or ADH deficiency or AVP deficiency).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 2. (posterior pituitary dysfunction or posterior pituitary deficit).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 3. 1 or 2 4. (brain tumour or brain tumor or brain neoplasm).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 5. (perioperative or postoperative).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 6. (neurosurgery or neurosurgical or surgery or surgical).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 7. 5 or 6 8. (water deprivation test or paired osmolality or paired osmolalities or urinary copeptin or plasma vasopressin or plasma antidiuretic hormone or plasma arginine-vasopressin or plasma ADH or plasma AVP).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 9. 3 and 4 and 7 and 8 10. 3 and 7 and 8 11. exp diabetes insipidus/ or exp diabetes insipidus, neurogenic/ 12. exp Brain Neoplasms/ 13. exp Perioperative Nursing/ or exp Perioperative Care/ or exp Perioperative Period/ 14. exp Postoperative Complications/ 15. 13 or 14 16. exp "Sensitivity and Specificity"/ or exp "Predictive Value of Tests"/ 17. exp Diagnosis/ 18. 16 or 17 19. 11 and 12 and 15 and 18 20. 10 or 19	151	13	10	2 (but see section 3.2.1.3.e-f for diagnostic criteria for central diabetes insipidus)

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Berton et al., 2020(179)	Prospective cohort	No	No	Yes: adult patients only, mixed cohort of tumours (4 craniopharyngiomas)	No	No	No	No	No

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Winzeler et al., 2015(180)	Prospective cohort	No	No	Yes: adult patients only, mixd cohort of tumours (9 craniopharyngiomas	No	No	No	No	No

Author(s)	Summary of findings					Quality
	No. of positive tests in CDI group	No. of patients	No. of positive tests in non-CDI group	No. of patients	Pooled effect	
Berton et al., 2020	N/A	N/A	N/A	N/A	1-hour postoperative plasma copeptin <12.8 pmol/l: Sensitivity 87.5% Specificity 76% 1-hour postoperative/ preoperative plasma copeptin ratio <1.47: Sensitivity 75% Specificity 78.8%	Very low
Winzeler et al., 2015	N/A	N/A	N/A	N/A	12-hour postoperative plasma copeptin <2.5 pmol/l: Sensitivity 44% Specificty 97% 12-hour postoperative plasma copeptin >30 pmol/l: Sensitivity 98% Specificity 25%	Very low

Outcome 3.2.2.2.d: Perioperative testing for SIADH

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years with craniopharyngiomas undergoing surgical procedures **I** how do the following (in combination or alone): • Paired urine/ plasma osmolalities (urine: plasma>1.5) • Urine specific gravity >1.010 • Oliguria <1 ml/kg/hour • Plasma sodium <132 mmol/l and urinary sodium 20-70 mmol/l • Plasma AVP • Urinary/ plasma copeptin **C** compared to a fluid restriction challenge leading to eunatraemia **O** in terms of sensitivity and specificity for detecting the syndrome of inappropriate diuretic hormone secretion **T** in the post-operative period?	1. (syndrome of inappropriate antidiuretic hormone or SIADH).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 2. (posterior pituitary dysfunction or posterior pituitary deficit).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 3. 1 or 2 4. (brain tumour or brain tumor or brain neoplasm).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 5. (perioperative or postoperative).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 6. (neurosurgery or neurosurgical or surgery or surgical).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 7. 5 or 6 8. (paired osmolality or paired osmolalities or urinary copeptin or plasma vasopressin or plasma arginine-vasopressin or plasma AVP or plasma antidiuretic hormone or plasma ADH).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 9. 3 and 4 and 7 and 8 10. 3 and 7 and 8 11. exp Water-Electrolyte Imbalance/ or exp Hyponatremia/ or exp Inappropriate ADH Syndrome/ 12. exp Brain Neoplasms/ 13. exp Perioperative Nursing/ or exp Perioperative Care/ or exp Perioperative Period/ 14. exp Postoperative Complications/ 15. 13 or 14 16. exp "Sensitivity and Specificity"/ 17. exp "Predictive Value of Tests"/ 18. exp Diagnosis/ 19. 16 or 17 or 18 20. 11 and 12 and 15 and 19 21. 10 or 20	67	10	6	2

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Cardoso et al., 2007(181)	Prospective cohort	No	No	Yes – mixed cohort of adults and children (4 <19 years), mixed cohort of tumours and aneurysms (no craniopharyngiomas)	Yes – small cohort	Yes – single centre	No	No	No
Sata et al., 2006(182)	Retrospective cohort	Yes – only transsphenoidal patients included, only examined 24/110 patients with hyponatraemia (i.e. no control group)	No	Yes – mixed cohort of adults and children, mixed cohort of tumours (5 craniopharyngiomas but none included in analysis)	Yes – small cohort, only 3 had SIADH	Yes – only included 24/110 patients with hyponatraemia post-transsphenoidal surgery	No	No	No

Author(s)	Summary of findings					Quality
	No. of positive tests in SIADH group	No. of patients	No. of positive tests in non-SIADH group	No. of patients	Pooled effect	
Cardoso et al., 2007	Plasma AVP >0.5 pg/ml: 3 Natriuresis (definition unclear): 1 Oliguria: 0	3	N/A	N/A	Unable to calculate as no control data	Very low
Sata et al., 2006	Urine: plasma osmolality >1: 24 Plasma AVP >0.21 pg/ml: 24	24 24	N/A	N/A	Unable to calculate as unclear what proportion of patients truly had SIADH	Very low

Outcome 3.2.2.2.d: Perioperative testing for cerebral salt-wasting syndrome

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years with craniopharyngiomas undergoing surgical procedures **I** how do the following (in combination or alone): • Paired urine/ plasma osmolalities (urine: plasma>1-1.5) • Urine specific gravity >1.010 • Polyuria >5 ml/kg/hour • Plasma sodium <132 mmol/l and urinary sodium >70 mmol/l **C** compared to a 0.9% NaCl IV fluid bolus challenge leading to polyuria **O** in terms of sensitivity and specificity for detecting cerebral salt-wasting **T** in the post-operative period?	1. (cerebral salt-wasting or cerebral salt wasting).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 2. (posterior pituitary dysfunction or posterior pituitary deficit).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 3. 1 or 2 4. (brain tumour or brain tumour or brain neoplasm).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 5. (perioperative or postoperative).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 6. (neurosurgery or neurosurgical or surgery or surgical).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 7. 5 or 6 8. (paired electrolytes or paired osmolality or paired osmolalities or atrial natriuretic peptide or atrial natriuretic factor or atrial natriuretic hormone or cardionatrine or cardiodilatine or ANP or ANF or ANH or atriopeptin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 9. 3 and 4 and 7 and 8 10. 3 and 7 and 8 11. exp Water-Electrolyte Imbalance/ 12. exp Hyponatremia/ 13. 11 or 12 14. exp Brain Neoplasms/ 15. exp Perioperative Nursing/ or exp Perioperative Care/ or exp Perioperative Period/ 16. exp Postoperative Complications/ 17. 15 or 16 18. exp "Sensitivity and Specificity"/ 19. exp "Predictive Value of Tests"/ 20. exp Diagnosis/ 21. 18 or 19 or 20 22. 13 and 14 and 17 and 2 23. 10 or 22	66	13	7	4

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Papadimitriou et al., 2007(186)	Case series	Yes – case series	No	Yes – one of two cases craniopharyngioma	Yes – small case series	Yes – case series of 2 patients	No	No	No

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Guerrero et al., 2007(185)	Case report	Yes – case report, patient also had hypotonic saline infusion prior to diagnosis	No	Yes – adult patient with pituitary adenoma	Yes – case report	Yes – case report	No	No	No
von Bismarck et al., 2006(187)	Case series	Yes – case series, hormonal measurements not uniformly measured	No	Yes – mixed cohort of aetiologies, none craniopharyngioma	Yes – small case series	Yes – case series of 9 patients	No	No	No
Yamaki et al., 1992(188)	Case series	Yes – case series, hormonal measurements not uniformly measured	No	Yes – adult patients with pituitary adenomas	Yes – small case series	Yes – case series of 2 patients	No	No	No

Author(s)	Summary of findings					Quality
	No. of positive tests in cerebral salt-wasting syndrome group	No. of patients	No. of positive tests in non-cerebral salt-wasting syndrome group	No. of patients	Pooled effect	
Papadimitriou et al., 2007	Serum sodium <132 mmol/l: 2 Low renin/ aldosterone: 2 Raised/ detectable BNP: 2 Raised/ detectable ANP: 1	2	N/A	N/A	N/A	Very low
Guerrero et al., 2007	Serum sodium <132 mmol/l: 1 Urine sodium > 70 mmol/l: 1	1	N/A	N/A	N/A	Very low
von Bismarck et al., 2006	Urine output >5 ml/kg/hr: 7 Urine sodium >70 mmol/l: 9 Raised ANP: 3 Raised BNP: 3 Low renin/ aldosterone: 4	9 9 6 7 5	N/A	N/A	N/A	Very low
Yamaki et al., 1992	Serum sodium <132 mmol/l: 2 Urine sodium >70 mmol/l: 2 Raised ANP: 0 Low aldosterone: 0	2 2 1 1	N/A	N/A	N/A	Very low

Outcome 3.2.2.3.a-c: Effectiveness of radiotherapy

(*note the literature search for both PICO questions were conducted simultaneously)

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years who have had complete resection of a craniopharyngioma **I** does upfront radiotherapy **C** compared to no upfront radiotherapy **O** improved overall and progression-free survival? **P** In children <19 years who have had incomplete (partial/ subtotal) resection of a craniopharyngioma **I** does upfront radiotherapy **C** compared to no upfront radiotherapy **O** improved overall and progression-free survival?	1. craniopharyngioma.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 2. radiotherapy.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 3. survival.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 4. 1 and 2 and 3 5. exp Craniopharyngioma/ 6. exp Radiotherapy/ or exp Radiotherapy, Adjuvant/ 7. exp Disease-Free Survival/ or exp Survival Analysis/ or exp Survival/ or exp Survival Rate/ 8. 5 and 6 and 7 9. 4 or 8 10. limit 9 to "all child (0 to 18 years)"	175	73	40	25

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Bishop et al., 2014(192)	Retrospective cohort	No	No	Yes – note study was aimed at assessing proton beam vs. conventional radiotherapy	No	No	No	Yes – multicentre study	No
Clark et al., 2013(126)	Systematic review of cohort studies	Yes – no multivariate analysis, tumour grade/ location not determined	No	Yes – does not answer question about timing of radiotherapy	No	No	No	Yes – multiple centres with different treatment strategies	No
Schoenfeld et al., 2012(130)	Retrospective cohort	Yes – single centre, no multivariate analysis, tumour grade/ location not determined	No	Yes – mixed cohort of adults and children (median age 30 (IQR 11-52) years), mixed cohort of craniopharyngioma histologies (65% adamantinomatous)	Yes – some confidence intervals very wide	Yes – single centre only	Yes – hazard ratios for STR vs. STR + radiotherapy >2, GTR vs. STR <0.5	No	No

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Zhao et al., 2012(137)	Retrospective cohort	Yes – single centre	No	Yes – mixed cohort of adults and children (median age 27 (range 21 months – 68 years), unclear proportion of different craniopharyngioma histologies, some patients with recurrent tumours	Yes – very wide confidence intervals	Yes – single centre only	Yes – hazard ratios for STR vs. GTR >2	No	No
Jeon et al., 2011(327)	Retrospective cohort	Yes – single centre, no multivariate analysis	No	Yes – mixed cohort of adults and children (median 33.6 years)	No	Yes – single centre only	No	No	No
Mortini et al., 2011(320)	Retrospective cohort	Yes – single centre, unclear if effects of radiotherapy were included in multivariate model	No	Yes – mixed cohort of adults and children (34 of 112 <18 years)	No	Yes – single centre only	Yes – hazard ratio for radiotherapy <0.5	No	No
Winkfield et al., 2011(190)	Retrospective cohort	Yes – single centre (but note change in treatment strategy over the eras)	No	No	Yes – wide confidence intervals	Yes – single centre	Yes – OR > 2 for radiotherapy	No	No
Yang et al., 2010(136)	Systematic review of cohort studies	Yes – no multivariate analysis, tumour grade/ location/ size not determined	No	Yes – mixed cohort of adults and children, unclear proportion of different histologies	No (but no confidence intervals reported)	No	No (but hazard ratios not reported)	Yes – multiple cohort studies in different centres with different strategies/ techniques	No
Lin et al., 2008(30)	Retrospective cohort	Yes – single centre	No	No	Yes – small cohort (31 patients)	Yes – single centre	No	No	No

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Combs et al., 2007(351)	Retrospective cohort	Yes – single centre, no direct comparison between radiotherapy + surgery vs. surgery alone, calculated survival from start of radiotherapy	No	Yes – mixed cohort of adults and children (6/40 <18 years), unclear types of histology treated	Yes – small cohort (40 patients)	Yes – single centre	No	No	No
Pemberton et al., 2005(352)	Retrospective cohort	Yes – single centre, no multivariate analysis incorporating initial surgical strategy	No	Yes – mixed cohort of adults and children (28/87 <15 years)	No	Yes – single centre	No	No	No
Moon et al., 2005(191)	Retrospective cohort	Yes – single centre, multivariate analysis unclear re: which variables included	No	Yes – mixed cohort of adults and children (median age 29 years), mixed cohort of histologies (12/50 adamatinomatous)	Yes – moderately small cohort	Yes – single centre	No	No	No
Karavitaki et al., 2005(24)	Retrospective cohort	Yes – single centre, no multivariate analysis	No	Yes – mixed cohort of adults and children (42/121 aged <16 years)	No	Yes – single centre	Yes – no HRs calculated but large apparent differences with highly significant p-values	No	No
Stripp et al., 2004(141)	Retrospective cohort	Yes – single centre, no multivariate analysis	No	Yes – mixed cohort of adults and children (median 8.5 years)	No	Yes – single centre	No	No	No
Fisher et al., 1998(62)	Retrospective cohort	Yes – single centre, unclear if multivariate analysis performed	No	No	Yes – small cohort (no confidence intervals reported)	Yes – single centre	No	No	No
Khafaga et al., 1998(353)	Retrospective cohort	Yes – single centre, no multivariate analysis	No	Yes – mixed cohort of primary and recurrent tumours	Yes – moderately small cohort	Yes – single centre	No	No	No

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Scott et al., 1994(354)*	Retrospective cohort	Yes – single centre, no multivariate analysis, did not factor in degree of resection	No	Yes – study >20 years old	Yes – moderately small cohort	Yes – single centre	No	No	No
Hetelekidis et al., 1993(29)*	Retrospective cohort	Yes – single centre, no multivariate analysis, did not factor in degree of resection	No	Yes – study >20 years old	Yes – moderately small cohort	Yes – single centre	No	No	No
Manaka et al., 1985(355)	Retrospective cohort	Yes – single centre, no multivariate analysis	No	Yes – mixed cohort of adults and children (mean 22.9 years), study >20 years old	No	Yes – single centre	No	No	No
Vyramuthu & Benton, 1983(356)	Retrospective cohort	Yes – single centre, no multivariate analysis	No	Yes – mixed cohort of adults and children (12/26 children), study >20 years old	Yes – small cohort	Yes – single centre	No	No	No
Carmel et al., 1982(357)	Retrospective cohort	Yes – single centre, no multivariate analysis	No	Yes – study >20 years old	Yes – moderately small cohort	Yes – single centre	No	No	No
Richmond et al., 1980(358)	Retrospective cohort	Yes – single centre, no multivariate analysis	Yes – cyst aspiration/ biopsy + radiotherapy had higher PFS compared to STR/ GTR +/- radiotherapy	Yes – study >20 years old	Yes – moderately small cohort	Yes – single centre	No	No	No
Shapiro et al., 1979(359)	Retrospective cohort	Yes – single centre, no multivariate analysis	No	Yes – study >20 years old	Yes – moderately small cohort	Yes – single centre	No	No	No
McMurry et al., 1977(360)	Retrospective cohort	Yes – single centre, no multivariate analysis	No	Yes – mixed cohort of adults & children (15/50 <18 years), study >20 years old	Yes – moderately small cohort	Yes – single centre	No	No	No

*Note data is from same study

Author(s)	Summary of findings					Quality
	No. of events in radiotherapy group	No. of patients	No. of events in non-radiotherapy group	No. of patients	Pooled effect	
Bishop et al., 2014	N/A	N/A	N/A	N/A	Salvage radiotherapy resulted in increased visual and endocrine dysfunction (both p<0.05) compared to adjuvant radiotherapy	Low
Clark et al., 2013	Recurrence: STR + radiotherapy 27	54	Recurrence: GTR alone 51 STR alone 51	145 79	5-year PFS: GTR alone 77% STR alone 43% STR + radiotherapy 73%	Moderate
Schoenfeld et al., 2012	2-year PFS: STR + radiotherapy 73% 10-year OS: STR + radiotherapy 96%	46 46	2-year PFS: GTR 75% STR 36% 10-year OS: GTR 96% STR 81%	33 37 33 37	Univariate PFS: GTR vs. STR + radiotherapy HR 1.24(0.62-2.49) STR vs. STR + radiotherapy HR 4.15(2.26-7.61) Univariate OS: GTR vs. STR + radiotherapy HR 0.66(0.06-7.40) STR vs. STR + radiotherapy HR 4.88(1.00-23.74)	Very low
Zhao et al., 2012	Progression/ recurrence: GTR + radiotherapy 3 STR + radiotherapy 32 Deaths: STR + radiotherapy 6	37 32 32	Progression/ recurrence: GTR 7 STR 13 Deaths GTR 7 STR 6	69 13 106 13	Multivariate OS: Radiotherapy 0.166 (0.026-1.056) No difference in recurrence rate GTR vs. GTR + radiotherapy Significant differences in recurrence rate for GTR +/- radiotherapy > STR + radiotherapy, STR > STR + radiotherapy	Very low
Jeon et al., 2011	Mean PFS: Salvage radiotherapy 106.2 months (79.0-133.3) Adjuvant radiotherapy 93.8 months (67.6-120.0)	21 29	N/A	N/A	No significant difference in PFS for salvage vs. adjuvant radiotherapy (note no analysis of timing of radiotherapy vs. long-term toxicities)	Very low
Mortini et al., 2011	Recurrence: STR + radiotherapy	8	Recurrence: GTR alone STR alone	82 19	?Univariate PFS: Radiotherapy HR 0.09 (0.01-0.76)	Very low
Winkfield et al., 2011	GTR + radiotherapy STR + radiotherapy Cyst aspiration + radiotherapy 10-year OS: 92% 10-year PFS: 84% Recurrence rates for all surgery + radiotherapy: Pre-1998 21% Post-1998 5%	1 24 18	GTR alone STR alone Cyst aspiration alone 10-year OS: 97% 10-year PFS: 52% Recurrence rates for all surgery alone: Pre-1998 63% Post-1998 36%	25 8 18	No difference in OS for surgery + radiotherapy vs. surgery alone Significant difference in PFS between radiotherapy > non-radiotherapy group, independent of treatment strategy Recurrence rate OR (multivariate) 7.7 (2.0-28.7) No difference in long-term toxicities between radiotherapy and non-radiotherapy group	Very low

Author(s)	Summary of findings					Quality
	No. of events in radiotherapy group	No. of patients	No. of events in non-radiotherapy group	No. of patients	Pooled effect	
Yang et al., 2010	5-year PFS: STR + radiotherapy 69% 10-year OS: STR + radiotherapy 95%	 85 85	5-year PFS: GTR 67% STR 34% 10-year OS: GTR 98% STR 93%	 256 101 256 101	PFS not significantly higher in GTR vs. STR + radiotherapy No significant differences in OS	Very low
Lin et al., 2008	Recurrence/ progression: STR/ cyst aspiration + radiotherapy 0	11	Recurrence/ progression: GTR alone 6 STR/ cyst aspiration alone 6	14 6	10-year local control rate Radiotherapy 100% No radiotherapy 32% Final local control rate: Adjuvant radiotherapy 100% Salvage radiotherapy 78%	Very low
Combs et al., 2007	STR/ cyst aspiration + radiotherapy	12	GTR alone STR/ cyst aspiration alone	7 21	Median 10-year PFS post-radiotherapy (both adjuvant and salvage) 100% No significant difference between adjuvant and salvage radiotherapy groups	Very low
Pemberton et al., 2005	20-year PFS: Adjuvant radiotherapy 73%	44	20-year PFS: Salvage radiotherapy 60%	43	No significant difference between adjuvant and salvage radiotherapy groups No increase in radiotherapy toxicity in children vs. adults	Very low
Moon et al., 2005	10-year PFS: Adjuvant radiotherapy 91.2% Deaths: Adjuvant radiotherapy 6 DDAVP supplementation: Adjuvant radiotherapy 38% Stable vision: Adjuvant radiotherapy 100%	25	10-year PFS: Salvage radiotherapy 91.3% Deaths: Salvage radiotherapy 2 DDAVP supplementation: Salvage radiotherapy 65% Stable vision: Salvage radiotherapy 38-50%	25	No significant difference in OS/PFS between adjuvant and salvage radiotherapy groups Significant increase in DDAVP supplementation and visual deterioration in salvage radiotherapy group	Very low
Karavitaki et al., 2005	20-year PFS: GTR + radiotherapy 100% STR + radiotherapy 77% 10-year visual deterioration: GTR + radiotherapy 0% STR + radiotherapy 24%	 3 33 3 33	20-year PFS: GTR alone 100% STR alone 32% 10-year visual deterioration: GTR alone 9% STR alone 45%	 16 51 16 51	No significant difference in OS No HRs calculated for PFS but difference between groups highly statistically significant No significant difference in endocrine/ neurological morbidity between groups, but higher incidence of visual morbidity with STR alone	Very low

Author(s)	Summary of findings					Quality
	No. of events in radiotherapy group	No. of patients	No. of events in non-radiotherapy group	No. of patients	Pooled effect	
Stripp et al. 2004	10-year PFS: STR + radiotherapy (adjuvant) 84%	18	10-year PFS: All surgery 42% GTR alone 47% STR alone 78% STR + radiotherapy (salvage)	 44 9 22	No HRs calculated but PFS significantly higher for STR + radiotherapy > GTR alone/ STR alone Note rate of DI GTR 88.4% vs. STR 65.4%	Very low
Fisher et al., 1998	N/A	N/A	N/A	N/A	Non-significant trend for improved PFS with adjuvant vs. salvage radiotherapy	Very low
Khafaga et al., 1998	N/A - study did not separate GTR vs. STR +/- radiotherapy in terms of outcomes	N/A	N/A	N/A	N/A	Very low
Scott et al., 1994	Recurrences: Radiotherapy alone 0 Surgery + radiotherapy 7 10-year PFS: Radiotherapy alone 100% Surgery + radiotherapy 86% 10-year OS: Radiotherapy alone 100% Surgery + radiotherapy 60%	 9 37	Recurrences: Surgery alone 9 10-year PFS: Surgery alone 31% 10-year OS: Surgery alone 100%	 15	Endocrine morbidity surgery alone > surgery + radiotherapy > radiotherapy alone	Very low
Hetelekidis et al., 1993	Same data as Scott et al., 1994					Very low
Manaka et al., 1985	10-year OS: Surgery then radiotherapy 80.6% Radiotherapy then surgery 57.1%	 34 7	10-year OS: Surgery only 27.1% Surgery then salvage radiotherapy 75.0%	 80 4	Significant difference in OS for radiotherapy vs. non-radiotherapy patients regardless of degree of resection in STR group	Very low
Vyramuthu & Benton, 1983	Recurrences: STR + radiotherapy 0 Cyst aspiration + radiotherapy 0 Deaths: STR + radiotherapy 0 Cyst aspiration + radiotherapy 0	 10 6 10 6	Recurrences: GTR alone 0 STR alone 3 Cyst aspiration alone 2 Deaths: GTR alone 2 STR alone 4	 3 4 4 3 4	No statistics performed	Very low
Carmel et al., 1982	Recurrence: STR/ cyst aspiration+ radiotherapy 3 Deaths: STR/ cyst aspiration + radiotherapy 1	 14 14	Recurrences: GTR alone 6 STR alone 13 Deaths: GTR alone 0 STR alone 8	 14 14 14 14	No statistics performed but PFS GTR = STR + radiotherapy > STR alone; OS GTR > STR + radiotherapy > STR alone	Very low

Author(s)	Summary of findings					Quality
	No. of events in radiotherapy group	No. of patients	No. of events in non-radiotherapy group	No. of patients	Pooled effect	
Richmond et al., 1980	Recurrences: STR + radiotherapy N/A Cyst aspiration + radiotherapy N/A Deaths: STR + radiotherapy 6 Cyst aspiration + radiotherapy 0 10-year OS: STR + radiotherapy 44% Cyst aspiration + radiotherapy 100%	 12 8 12 8	Recurrences: GTR alone 3 STR alone N/A Deaths: GTR alone 2 STR alone 2 10-year OS: GTR alone 50% STR alone 50%	 8 4 8 4	No statistics performed	Very low
Shapiro et al., 1979	Recurrences: STR + radiotherapy 0 Cyst aspiration + radiotherapy 11 8-year PFS STR + radiotherapy 85% Cyst aspiration + radiotherapy 50%	 7 22	Recurrences: GTR alone 5 STR alone 7 8-year PFS: GTR alone 74% STR alone 40%	 22 9	PFS for GTR alone = STR + radiotherapy > cyst aspiration + radiotherapy > STR alone	Very low
McMurry et al., 1977	Deaths: STR + radiotherapy 2	 11	Deaths: GTR alone 4 STR 7	 10 9	No statistics performed	Very low

Outcome 3.2.2.3.d-f: Optimum radiotherapy regimen

(*note the literature search for both PICO questions were conducted simultaneously)

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years undergoing radiotherapy for craniopharyngiomas **I** what are the best doses/ tumour volumes for radiotherapy **O** leading to increased overall and progression-free survival? **P** In children <19 years undergoing radiotherapy for craniopharyngiomas **I** do the following total doses and fractions: • 44 Gy/ 54 Gy/ 55.8 Gy/ 66 Gy • 1.8 Gy fractions/ 2.0 Gy fractions/ 3.3 Gy fractions **O** influence overall and progression-free survival, the incidence of radiation necrosis, the incidence of cognitive, visual and hypothalamo-pituitary dysfunction, or the incidence of second malignant neoplasms?	1. craniopharyngioma.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 2. radiotherapy.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 3. (dose or dosage or dosimetry).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 4. (fraction or fractionation or hypofractionation or hyperfractionation).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 5. (clinical target volume or CTV or gross tumour volume or gross tumor volume or GTV or margin*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 6. 3 or 4 or 5 7. 1 and 2 and 6 8. exp Craniopharyngioma/ 9. exp Radiotherapy, High-Energy/ or exp Radiotherapy, Computer-Assisted/ or exp Radiotherapy, Image-Guided/ or exp Radiotherapy Planning, Computer-Assisted/ or exp Radiotherapy, Adjuvant/ or exp Radiotherapy, Intensity-Modulated/ or exp Radiotherapy, Conformal/ or exp Radiotherapy/ or exp Radiotherapy Dosage/ 10. exp Dose Fractionation/ 11. exp Radiation/ or exp Radiation Dosage/ 12. 9 or 10 or 11 13. 8 and 12 14. 7 or 13 15. limit 14 to (english language and "all child (0 to 18 years)")	368	62	42	2 (insufficient data to provide full recommendation therefore Delphi consensus)

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Merchant et al., 2013(193)	Prospective cohort	No	No	No	No	Yes – single centre	No	Yes – examined multiple factors affecting PFS	No
Regine et al., 1993(198)	Retrospective cohort	No	No	Yes – mixed cohort of adults and children (19/58 <16 years), study >20 years old	No	Yes – single centre	No	No	No

Author(s)	Summary of findings					Quality
	No. of events in intervention group	No. of patients	No. of events in control group	No. of patients	Pooled effect	
Merchant et al., 2013	5-year PFS: CTV ≤5 mm 96.2%	62	10-year PFS: CTV >5 mm 88.1%	26	No significant differences in PFS based on differences in 95% target volume coverage	Low
Regine et al., 1993	Recurrences: ≤54 Gy 3	6	Recurrences: >54 Gy 2	13	No statistics performed	Very low

Outcome 3.2.2.3.g: Efficacy of proton beam therapy (PBT)

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years undergoing radiotherapy for craniopharyngiomas **I** does proton beam therapy **C** compared to conventional photon-based irradiation techniques **O** lead to equivalent overall and progression-free survival, reduced cognitive/ IQ impairment, reduced visual impairment, or reduced hypothalamo-pituitary dysfunction?	1. craniopharyngioma.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 2. (proton or protons).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 3. 1 and 2 4. exp Craniopharyngioma/ 5. exp Proton Therapy/ 6. 4 and 5 7. 3 or 6 8. limit 7 to (english language and "all child (0 to 18 years)")	57	11	7	3

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Leroy et al., 2016(202)	Systematic review of cohort studies	No	No	No	No	No	No	Yes – multiple centres with different treatment regimens	No
Bishop et al., 2014(192)	Retrospective cohort	Yes – note significant differences in follow-up duration between PBT and conventional groups	No	No	No	No	No	Yes – multicentre study	No
Merchant et al., 2008(203)	Retrospective cohort	No – but note only modeling data	No	Yes – mixed cohort of paediatric brain tumours (10 craniopharyngioma)	No	No	No	No	No

Author(s)	Summary of findings					Quality
	No. of events in PBT group	No. of patients	No. of events in conventional radiotherapy group	No. of patients	Pooled effect	
Leroy et al., 2016	N/A	N/A	N/A	N/A	No pooled meta-analysis performed but overall no differences in OS or PFS	Low

Author(s)	Summary of findings					Quality
	No. of events in PBT group	No. of patients	No. of events in conventional radiotherapy group	No. of patients	Pooled effect	
Bishop et al., 2014	Cyst growth 6 3-year cystic PFS 67.0% 3-year solid PFS 91.7% 3-year OS 94.1%	21	Cyst growth 4 3-year cystic PFS 76.8% 3-year solid PFS 96.4% 3-year OS 96.8%	31	No significant independent contribution of radiotherapy modality to PFS/ OS No differences in neurological, visual or endocrine morbidity between PBT and conventional groups (note differences in lengths of follow-up)	Low
Merchant et al., 2008	N/A	N/A	N/A	N/A	No actual clinical outcome data – note only modelled radiation doses and estimated IQ losses	Very low

Outcome 3.2.2.3.h: Efficacy of stereotactic radiosurgery (SRS)

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years undergoing radiotherapy for craniopharyngiomas **I** does primary stereotactic radiosurgery **C** compared to complete resection, incomplete resection with upfront conventional radiotherapy or radiotherapy alone **O** lead to equivalent overall and progression-free survival, reduced cognitive/ IQ impairment, reduced visual impairment, or reduced hypothalamo-pituitary dysfunction?	1. craniopharyngioma.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 2. radiosurgery.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 3. gamma knife.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 4. 2 or 3 5. 1 and 4 6. exp Craniopharyngioma/ 7. exp Radiosurgery/ 8. 6 and 7 9. 5 or 8 10. limit 9 to (english language and "all child (0 to 18 years)")	124	55	36	9

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Niranjan et al., 2010(206)	Retrospective cohort	Yes – single centre, no multivariate analysis, all previously treated tumours with various modalities, no comparison group	No	Yes – mixed cohort of adults and children (but median age 23.5 years), all previously treated tumours with various modalities	No	Yes – single centre	No	No	No
Hasegawa et al., 2010(209)	Retrospective cohort	Yes – single centre, 96% previously treated tumours, no comparison group	No	Yes – mixed cohort of adults and children (40/100 <15 years), 96% previously treated tumours with various modalities	No	Yes – single centre	No	No	No
Kobayashi, 2009(210)	Retrospective cohort	Yes – single centre, majority/ all previously treated tumours, no comparison group	No	Yes – mixed cohort of adults and children (38/98 <15 years), majority/ all previously treated tumours	No	Yes – single centre	No	No	No

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Kobayashi et al., 2005(212)	Retrospective cohort	Yes – single centre, majority/ all previously treated tumours, no comparison group	No	Yes – mixed cohort of adults and children (38/98 <15 years), majority/ all previously treated tumours	No	Yes – single centre	No	No	No
Kobayashi et al., 2003(211)	Retrospective cohort	Yes – single centre, majority/ all previously treated tumours, no comparison group	No	Yes – mixed cohort of adults and children (38/98 <15 years), majority/ all previously treated tumours	No	Yes – single centre	No	No	No
Amendola et al., 2003(207)	Case series	Yes – single centre, majority recurrent tumours, no comparison group	No	Yes – mixed cohort of adults and children (but 12/14 <21 years), 12/14 recurrent tumours	Yes – case series	Yes – single centre case series, only 14 cases	No	No	No
Ulfarsson et al., 2002(214)	Case series	Yes – single centre, no comparison group, treatment involved combined SRS and brachytherapy	No	Yes – mixed cohort of adults and children (11/21 <15 years), mixed cohort of primary and recurrent tumours (8 primary)	Yes – case series	Yes – single centre case series, only 14 cases	No	No	No
Chung et al., 2000(208)	Retrospective cohort	Yes – single centre, no comparison group, majority/ all previously treated tumours	No	Yes – mixed cohort of adults and children (9/31 <16 years), mixed cohort of previous treatment modalities	Yes – small cohort	Yes – single centre	No	No	No
Mokry, 1999(213)	Retrospective cohort	Yes – single centre, no comparison group, all previously treated tumours	No	Yes – mixed cohort of adults and children (8/23 <15 years), all with previous treatment modalities	Yes – relatively small cohort of 23 patients	Yes – single centre	No	No	No

Author(s)	Summary of findings					Quality
	No. of events in SRS group	No. of patients	No. of events in conventional radiotherapy group	No. of patients	Pooled effect	
NIranjan et al., 2010	Deaths 5 Progression 20 5-year PFS 67.8%	46	No comparison group	N/A	No comparison group	Very low
Hasegawa et al., 2010	Deaths 19 10-year OS 88% Progression 35 10-year PFS 52% 10-year local control 60% Visual deterioration 16	100	No comparison group	N/A	No comparison group	Very low
Kobayashi, 2009	Progression 20 Deaths 16	98	No comparison group	N/A	No comparison group	Very low
Kobayashi et al., 2005	Same data as Kobayashi, 2009					
Kobayashi et al., 2003	Same data as Kobayashi, 2009					
Amendola et al., 2003	Local control 12 Deaths 0	14	No comparison group	N/A	No comparison group	Very low
Ulfarsson et al., 2002	Progression 14 Local control 7 Visual deterioration 8 Endocrine deterioration 4 Deaths 8	21	No comparison group	N/A	No comparison group but note 9/11 children progressed compared to 5/10 adults	Very low
Chung et al., 2000	Progression 4 Visual deterioration 1 Deaths 3	31	No comparison group	N/A	No comparison group	Very low
Mokry 1999	Progression 7 Deaths 2	23	No comparison group	N/A	No comparison group	Very low

Outcome 3.2.2.4.a: Efficacy of intracystic chemotherapies as primary treatment

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years with cystic craniopharyngiomas **I** does primary intracystic instillation of bleomycin, IFNα or radioisotopes **C** compared to primary resection/ primary cyst aspiration and drainage/ radiotherapy or conservative management **O** result in equivalent overall and progression-free survival, reduced cognitive/ IQ impairment, reduced visual impairment and reduced hypothalamo-pituitary dysfunction?	1. craniopharyngioma*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 2. (intracystic or cyst).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 3. (bleomycin or radioisotope or radionuclide or yttrium or phosphorus or interferon).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 4. 2 or 3 5. 1 and 4 6. exp Craniopharyngioma/ 7. exp Bleomycin/ 8. exp Radioisotopes/ 9. exp Interferons/ 10. 7 or 8 or 9 11. 6 and 10 12. 5 or 11 13. limit 12 to (english language and humans and "all child (0 to 18 years)")	405	70	17	8

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Kilday et al., 2017(218)	Retrospective cohort	Yes – non-randomised data, only tumours selected for treatment with intracystic therapies included, majority with previous therapies	No	Yes – mixed cohort of primary and recurrent tumours (77% recurrent)	No	No	Yes – time to progression 1.3 vs. 0.3 years	No	No
Zhang et al., 2016(222)	Meta-analysis of RCTs	Yes – only one RCT included which was at high risk of bias	No	Yes – only one RCT included which compared intracystic bleomycin with ^{32}P, with only 7 children	Yes – only one small single-centre RCT included	No	No	No	No
Zheng et al., 2014(223)	Meta-analysis of RCTs	Yes – only one RCT included	No	Yes – only one RCT included	Yes – only one small single-	No	No	No	No

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
		which was at high risk of bias		which compared intracystic bleomycin with ^{32}P, with only 7 children	centre RCT included				
Fang et al., 2012(220)	Meta-analysis of RCTs	Yes – only one RCT included which was at high risk of bias	No	Yes – only one RCT included which compared intracystic bleomycin with ^{32}P, with only 7 children	Yes – only one small single-centre RCT included	No	No	No	No
Liu et al., 2012(221)	Meta-analysis of RCTs	Yes – only one RCT included which was at high risk of bias	No	Yes – only one RCT included which compared intracystic bleomycin with ^{32}P, with only 7 children	Yes – only one small single-centre RCT included	No	No	No	No
Cavalheiro et al., 2010(217)	Prospective cohort	Yes – no comparison group, mixed primary and recurrent tumours	No	Yes – mixed cohort primary and recurrent tumours	No	No	No	No	
Lena et al., 2005(225)	Retrospective cohort	Yes – single centre	No	No	Yes – only 5/53 children treated with intracystic bleomycin	Yes – single centre	No	No	No
Mottolese et al., 2005(226)	Retrospective cohort	Yes – single centre	No	Yes – mixed cohort of primary and recurrent tumours	Yes – moderately small cohort (24/60) treated with intracystic bleomycin	Yes – single centre	No	No	No
Hukin et al., 2005(224)	Retrospective cohort	Yes – single centre	No	No	Yes – moderately small cohort with only 8/29 treated with intracystic bleomycin	Yes – single centre	No	No	No

Author(s)	Summary of findings					Quality
	No. of events in treatment group	No. of patients	No. of events in control group	No. of patients	Pooled effect	
Kilday et al., 2017	Cystic craniopharyngioma 15 Mixed solid/ cystic craniopharyngioma 20	16 26	Cystic craniopharyngioma 16 Mixed solid/ cystic craniopharygioma 25	16 26	<u>Median difference in time to progression:</u> Cystic craniopharyngioma 1.0 years Mixed solid/ cystic craniopharyngioma 0.2 years	Very low

Author(s)	Summary of findings					Quality
	No. of events in treatment group	No. of patients	No. of events in control group	No. of patients	Pooled effect	
Zhang et al., 2016	Mean reduction in cyst size 50.7% Adverse events 500 per 1000	3	Mean reduction in cyst size 65.5% Adverse events 875 per 1000	4	Mean difference -15% (-69-39%) Adverse events RR 1.75 (0.68-4.53) No reports on OS/ PFS	Very low
Zheng et al., 2014	Same data as Zhang et al., 2016					
Fang et al., 2012	Same data as Zhang et al., 2016					
Liu et al., 2012	Same data as Zhang et al., 2016					
Cavalheiro et al., 2010	Local control 47 Adverse effects 18	60	No comparison group	N/A	N/A	Very low
Lena et al., 2005	Recurrence 2	5	<u>Recurrence:</u> GTR alone 7 STR +/- radiotherapy/ SRS 9	 27 14	N/A	Very low
Mottolese et al., 2005	Local control 18 Deaths 0	24	Deaths 4	36	N/A	Very low
Hukin et al., 2005	Local control 3	8	<u>Local control:</u> GTR 9 GTR + radiotherapy 0 STR 1 STR + radiotherapy 4 Radiotherapy 3	 9 2 1 6 3	N/A	Very low

Outcome 3.2.2.4.a: Efficacy of systemic interferon-α

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years with cystic craniopharyngiomas **I** does primary systemic interferon-α **C** compared to primary resection/ radiotherapy/ conservative management **O** result in equivalent overall and progression-free survival, reduced cognitive/ IQ impairment, reduced visual impairment and reduced hypothalamo-pituitary dysfunction?	1. craniopharyngioma*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 2. interferon.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 3. 1 and 2 4. exp Craniopharyngioma/ 5. exp Interferons/ 6. 4 and 5 7. 3 or 6 8. limit 7 to english language	28	3	1	0 (decision made not to take forward to Delphi consensus)

Outcome 3.2.2.5.a: Optimum MRI follow-up interval

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years who have been treated/ conservatively managed for craniopharyngiomas **I** does serial MRI scanning every 3, 6, 12 months for 5, 10, 20 years **O** influence the sensitivity and specificity for detecting early tumour progression?	1. craniopharyngioma*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 2. (magnetic resonance imaging or MRI).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 3. (frequency or regular or interval).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 4. 1 and 2 and 3 5. exp Craniopharyngioma/ 6. exp Magnetic Resonance Imaging/ 7. exp Follow-Up Studies/ 8. 5 and 6 and 7 9. 4 or 8 10. limit 9 to (english language and "all child (0 to 18 years)")	139	4	2	2

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Shi et al., 2012(239)	Retrospective cohort	Yes – retrospective cohort, no definitive post-radiotherapy MRI protocol	No	Yes – mixed cohort of adults and children (median age 8.2 years)	Yes – small cohort of 21 cases	No	No	No	No
Hamamoto et al., 2002(238)	Retrospective cohort	Yes – retrospective cohort, no definitive post-radiotherapy MRI protocol	No	Yes – mixed cohort of adults and children (mean 37 years)	Yes – small cohort of only 8 patients	No	No	No	No

Author(s)	Summary of findings					Quality
	No. of events in frequent MRI group	No. of patients	No. of events in annual MRI group	No. of patients	Pooled effect	
Shi et al., 2012	N/A	N/A	N/A	N/A	Median time to maximal tumour expansion 1.5 months (range 1-5) Median time to maximal tumour shrinkage 9.5 months (range 3.5-39.9)	Very low
Hamamoto et al., 2002	N/A	N/A	N/A	N/A	Median time to tumour expansion 2 months (range 1-15 months) Mean time to tumour shrinkage 29.1 months (range 6-68 months)	Very low

Outcome 3.2.2.5.b: Optimum follow-up imaging interval post-radiotherapy

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years undergoing radiotherapy for craniopharyngiomas **I** is a follow-up MRI scan at 1, 2, 3, 4 or 6 months **C** compared to an MRI scan at 1 year **O** more sensitive and specific for detecting tumour volume changes and therefore response to treatment?	1. craniopharyngioma*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 2. radiotherapy.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 3. (magnetic resonance imaging or MRI).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 4. 1 and 2 and 3 5. exp Craniopharyngioma/ 6. exp Radiotherapy, Intensity-Modulated/ or exp Radiotherapy/ or exp Radiotherapy, Conformal/ or exp Radiotherapy, Image-Guided/ or exp Radiotherapy, Adjuvant/ 7. exp Magnetic Resonance Imaging/ 8. 5 and 6 and 7 9. 4 or 8 10. limit 9 to (english language and "all child (0 to 18 years)")	118	3	3	1 (insufficient date to provide recommendation therefore Delphi consensus)

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Shi et al., 2012(239)	Retrospective cohort	Yes – retrospective cohort, no definitive post-radiotherapy MRI protocol, variable doses of irradiation	No	Yes – mixed cohort of adults and children (median age 8.2 years)	Yes – small cohort of 21 cases	No	No	No	No

Author(s)	Summary of findings					Quality
	No. of events in early MRI group	No. of patients	No. of events in annual MRI radiotherapy group	No. of patients	Pooled effect	
Shi et al., 2012	N/A	N/A	N/A	N/A	Median time to maximal tumour expansion 1.5 months (range 1-5) Median time to maximal tumour shrinkage 9.5 months (range 3.5-39.9)	Very low

Outcome 3.2.2.5.c-d: Optimum protocol for visual surveillance

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years who have been treated/ conservatively managed for craniopharyngiomas **I** do regular assessments using visual acuity, visual field perimetry, VEPs, ERGs, OCT **C** compared to radiological surveillance **O** lead to an increased sensitivity and specificity for detecting early tumour progression and/ or early visual deterioration?	1. craniopharyngioma*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 2. (vis* or visual acuity or field perimetry or visual evoked potential* or electroretinogram* or optical coherence tomography or VA or VF or VEP or ERG or OCT).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 3. (magnetic resonance imaging or MRI or computed tomography or CT or CAT).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 4. (progression or survival).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 5. 1 and 2 and 3 and 4 6. exp Craniopharyngioma/ 7. exp Visual Fields/ or exp Visual Perception/ or exp Evoked Potentials, Visual/ or exp Visual Acuity/ or exp Visual Field Tests/ 8. exp Tomography, Optical Coherence/ 9. exp Electroretinography/ 10. exp Vision, Ocular/ 11. 7 or 8 or 9 or 10 12. exp Magnetic Resonance Imaging/ or exp Tomography, X-Ray Computed/ 13. exp Disease Progression/ 14. exp Disease-Free Survival/ or exp Survival Analysis/ or exp Survival/ or exp Survival Rate/ 15. 13 or 14 16. 6 and 11 and 12 and 15 17. 5 or 16 18. limit 17 to (english language and "all child (0 to 18 years)")	40	4	0	0 (therefore Delphi consensus)

Outcome 3.2.2.5.e-f: Optimum protocol for endocrine surveillance

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years who have been treated/ conservatively managed for hypothalamo-pituitary tumours I does an annual formal pituitary function test (e.g. ITT/ LHRH/ TRH) in all patients or only in patients at high risk of endocrine dysfunction C compared to testing based on clinical symptoms and signs O have an increased sensitivity and specificity for detecting early tumour progression and/ or early progression of endocrine dysfunction?	1. (brain tumour* or brain tumor* or brain neoplasm*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 2. (pituitary function test* or insulin tolerance test* or insulin stress test* or glucagon or clonidine or arginine or GHRH).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 3. (synacthen or synthetic adrenocorticotrophic hormone or synthetic adrenocorticotropic hormone or synthetic ACTH or cosyntropin or tetracosactide).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 4. (luteini*ing hormone releasing hormone or LHRH or gonadotrophin releasing hormone or gonadotropin releasing hormone or GnRH or triptorelin or gonadorelin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 5. (thyrotrophin releasing hormone or thyrotropin releasing hormone or TRH).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 6. 2 or 3 or 4 or 5 7. (annual or regular or monthly or screen* or protocol* or guideline*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 8. 1 and 6 and 7 9. exp Brain Neoplasms/ 10. exp Hypopituitarism/ 11. exp Diagnosis/ or exp Early Diagnosis/ 12. exp Mass Screening/ 13. exp Practice Guideline/ or exp Guideline/ 14. 12 or 13 15. 9 and 10 and 11 and 14 16. 9 and 10 and 14 17. 8 or 15 or 16	42	3	0	0 (therefore Delphi consensus)

Outcome 3.2.2.5.g: Effect of recombinant human growth hormone (rhGH) on tumour progression/ recurrence

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years with craniopharyngiomas and known GH deficiency/ insufficiency **I** does treatment with GH in replacement doses during active treatment, at the end of active treatment, 1+ year after the end of active treatment **C** compared to no treatment **O** reduce overall and progression-free survival?	1. craniopharyngioma*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 2. (growth hormone deficiency or GH deficiency or growth hormone insufficiency or GH insufficiency).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 3. (recurren* or relaps* or progress*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 4. (therap* or treat* or supplement*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 5. (human growth hormone or hGH or recombinant growth hormone or rhGH).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 6. 4 and 5 7. 1 and 2 and 3 and 6 8. 1 and 2 and 3 and 5 9. exp Craniopharyngioma/ 10. exp Growth Hormone/ 11. exp Recurrence/ 12. exp Disease Progression/ 13. 11 or 12 14. 9 and 10 and 13 15. 7 or 8 or 14 16. (brain tumour* or brain tumor* or brain neoplasm*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 17. exp Brain Neoplasms/ 18. 2 and 3 and 6 and 16 19. 2 and 3 and 5 and 16 20. 10 and 13 and 17 21. 15 or 18 or 19 or 20 22. limit 21 to (english language and "all child (0 to 18 years)")	43	17	13	7

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Boekhoff et al., 2018(247)	Prospective cohort	Yes – no multivariate analysis	No	No	Yes – wide interquartile ranges	No	No	No	No
Olsson et al., 2012(246)	Prospective case-control	No	No	Yes – mixed cohort of adults and children (mean age at diagnosis 25.1/ 32.3 years)	No	No	No	Yes – two-centre, multivariate analysis accounted for most treatment-related factors	No
Mackenzie et al., 2011(249)	Retrospective case-control	No	No	Yes – mixed cohort of adults and children (83/157 <16 years), mixed cohort of brain tumours (10/110 craniopharyngiomas)	No	No	No	Yes – controls matched for tumour type and radiation dose	
Muller et al., 2010(134)	Prospective cohort	Yes – note relatively short follow-up duration (3 years)	No	No	No	No	No	Yes – multicentre, multi-country study with multivariate analysis	No
Darendeliler et al., 2006(254)	Retrospective cohort (pharmacovigilance study)	Yes – only included rhGH-treated patients	No	No (mixed cohort of tumours but analysed separately)	No	No	No	Yes – multicenter, multi-country study	No
Karavitaki et al., 2006(248)	Retrospective case-control	No	No	No (mixed cohort of adults and children but age at diagnosis included in multivariate analysis)	No	No	No	Yes – multivariate analysis accounted for tumour treatment and age at diagnosis	No
Moshang et al., 1996(253)	Retrospective cohort (pharmacovigilance study)	Yes – only included rhGH-treated patients	No	No (mixed cohort of tumours but analysed separately)	No	No	No	Yes – multi-centre, multi country study	No

Author(s)	Summary of findings					Quality
	No. of events in rhGH group	No. of patients	No. of events in non-rhGH group	No. of patients	Pooled effect	
Boekhoff et al., 2018	10-year PFS: Childhood treated GH 32 ± 14% Adult treated GH 47 ± 25% Continuously treated GH 69 ± 11%	23 8 28	10-year PFS: No GH 50 ± 35%	6	p-values non-significant	Low
Olsson et al., 2012	Recurrences 9 10-year PFS 88%	56	Recurrences 30 10-year PFS 57%	70	HR 0.57 (0.26-1.3)	Low
Mackenzie et al., 2011	Recurrences 6 Second tumours 5	110	Recurrences 8 Second tumours 3	110	p-values non-significant	Low
Muller et al., 2010	N/A	54	N/A	60	p-value non-significant	Low
Darendeliler et al., 2006	121 10-year PFS 63%	1038	N/A	N/A	No association between duration of GH therapy and recurrence	Low
Karavitaki et al., 2006	Recurrences 4	32	Recurrences 22	53	rhGH HR 0.31 (0.09-1.04) Duration of rhGH HR 0.99/month (0.98-1.00)	Moderate
Moshang et al., 1996	Recurrences 35	546	N/A	N/A	Recurrence rate lower than previously published cohorts	Low

Outcome 3.2.2.5.i: Efficacy of treatments for hypothalamic obesity

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years who have been treated/ conservatively managed for hypothalamo-pituitary tumours with obesity **I** do the following therapies – dietary caloric restriction, increased physical activity, metformin, orlistat, sibutramine, dextroamphetamine, octreotide, GLP-1 agonists, triiodothyronine, gastric banding/ bypass surgery, early GH therapy **C** compared to no treatment or late commencement of GH **O** result in reduced BMI **T** at 6 months, 1 year, 2 years, and 5 years from commencing treatment?	1. hypothalamic obesity.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 2. (treat* or manag* or therap*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 3. 1 and 2 4. exp Obesity/ or exp Obesity, Morbid/ or exp Pediatric Obesity/ 5. exp Hypothalamus/ or exp Pituitary Neoplasms/ or exp Craniopharyngioma/ or exp Hyperphagia/ or exp Hypothalamic Diseases/ 6. exp Anti-Obesity Agents/ or exp Appetite Depressants/ or exp Fenfluramine/ 7. exp Metformin/ 8. exp Weight Loss/ 9. exp Diet/ or exp Diet Therapy/ 10. exp Dextroamphetamine/ 11. exp Gastric Bypass/ or exp Gastroplasty/ 12. exp Triiodothyronine/ 13. exp Thyroxine/ 14. exp Growth Hormone/ 15. exp Octreotide/ 16. exp Diazoxide/ 17. 4 and 5 18. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 19. 17 and 18 20. 3 or 19 21. limit 20 to (english language and "all child (0 to 18 years)")	383	24	17	15

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
van Schaik et al., 2020(268)	Case series	Yes – case series	No	No	Yes – case series of only 5 patients	Yes – case series	No	No	No
Horne et al., 2020(264)	Case series	Yes – case series	No	No	Yes – case series of only 12 patients	Yes – case series	No	No	No
van Santen et al., 2015(259)	Case report	Yes – case report	No	No	Yes – case report	Yes – case report	No	No	No
Ando et al., 2014(266)	Case series	Yes – case series	No	Yes – both adult patients, non-tumour causes for hypothalamic injury	Yes – case series of only 2 patients	Yes – case series	No	No	No

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Bretault et al., 2013(270)	Meta-analysis of case reports/ series	Yes – case reports and series only, varying bariatric techniques used	No	Yes – mixed cohort of adults and children (15/21 diagnosed <19 years, 9/21 had bariatric surgery <19 years)	Yes – only 21 patients included	No	Yes – large mean weight difference	Yes – multi-centre, multicountry analysis	No
Zoicas et al., 2013(267)	Case series	Yes – case series	No	Yes – mixed cohort of adults and children (1/9 diagnosed <19 years, all had bariatric surgery >19 years)	Yes – case series of only 9 patients	Yes – case series	Yes – large mean weight difference	No	No
Page-Wilson et al., 2012(361)	Case report	Yes – case report	No	Yes – bariatric surgery performed as an adult	Yes – case report	Yes – case report	No	No	No
Muller et al., 2011(362)	Case series	Yes – case series	No	Yes – 2/4 LAGB procedures performed in adulthood	Yes – case series of only 4 patients	Yes – case series	No	No	No
Rhakshani et al., 2010(269)	Prospective case-control	Yes – mixed case-control study (control cohort was historical and not matched for some cases)	No	No	No	No	No	No	No
Danielsson et al., 2007(265)	Randomised controlled crossover trial	Yes – relatively short duration of follow-up (68 weeks total)	No	Yes – mixed cohort of hypothalamic (22) and non-hypothalamic (28) obesity	No	No	No	Yes – randomised, double-blind, placebo-controlled study	No
Ismail et al., 2006(262)	Retrospective cohort	Yes – no control group	No	No	Yes – small cohort of only 12 patients	Yes – small cohort	No	No	No
Lustig et al., 2003(260)	Randomised controlled trial	Yes – short duration of follow-up	No	Yes - 2/20 non-brain tumour patients were post-radiotherapy for ALL	Yes – small cohort (18 subjects)	No	No	Yes – randomised, double-blind, placebo-controlled study	No
Fernandes et al., 2002(258)	Case series	Yes – case series, note treatment cause biochemical hyperthyroidism	No	Yes – mixed cohort of adults and children (2/3 children)	Yes – case series of only 3 patients	Yes – case series	Yes – large amounts of weight loss achieved	No	No
Mason et al., 2002(263)	Prospective cohort	Yes – no control group	No	No	Yes – small cohort of only 5 patients	Yes – small cohort	No	No	No

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Lustig et al., 1999(261)	Prospective cohort	Yes – no control group, short duration of follow-up, caloric intake data by recall	No	Yes – 2/9 were non-brain tumour patients post-radiotherapy for ALL	Yes – small cohort of only 9 patients	Yes – small cohort	No	No	No

Author(s)	Summary of findings					Quality
	Change in intervention group	No. of patients	Change in control group	No. of patients	Pooled effect	
van Schaik et al., 2020	BMI SDS +0.005 Absolute weight +1.5 kg Only 1 experienced weight loss	5	N/A	N/A	Duration of treatment: mean 8.4 years	Very low
Horne et al., 2020	ΔBMI rate of change -69.9%	12	N/A	N/A	Duration of treatment: median 3.1 years	Very low
van Santen et al., 2015	REE: -1.2 kcal/kg No change in body weight	1	N/A	N/A	Duration of treatment: 2 months	Very low
Ando et al., 2014	Weight: -3 and -11 kg HbA1c: -1.5% and -1.6%	2	N/A	N/A	Duration of treatment: 2 years	Very low
Bretault et al., 2013	<u>Mean % weight loss (absolute weight loss):</u> LAGB: -6.1% (-7.5 kg (95% CI -28.2-+13.2)) Sleeve gastrectomy: -19.6% (-25.9 kg (95% CI -59.7-+7.9)) Roux-en-Y: -20.2% (-33.7 kg (95% CI -80.7-+13.3) Biliopancreatic diversion: -24.8%	6 8 6 1	N/A	N/A	Mean weight difference (all techniques) -15.1 kg (95% CI -31.7-+1.4) Prevalence of diabetes -23.3%	Very low
Zoicas et al., 2013	Mean weight -13.1±5.1 kg Mean HOMA-IR -3.2±3.5 Mean HbA1c -1.3±1.4%	9	N/A	N/A	Duration of treatment 24.3±18.9 months (range 6-51 months)	Very low
Page-Wilson et al., 2012	Weight -31 kg REE -3.5 kcal/kg	1	N/A	N/A	Duration of follow-up 15 months	Very low
Muller et al., 2011	Mean BMI +4.1 kg/m^2 (range +1.7 - +8.7 kg/m^2)	4	N/A	N/A	Duration of follow-up 5.2-9.1 years	Very low
Rakhshani et al., 2010	Median BMI +4.5 kg/m^2/year (range -17.8-+8.4) Median BMI SDS 0.0/year (range -5.2-+0.5) Median % weight gain +8.5%/year (range +3.4-+14.0) Median % ideal body weight -4%/year (range -141.7-+34)	39	Median BMI +8.4 kg/m^2/year (range -3.1-+28.1) Median BMI SDS +0.4/year (range -2.1-+2.2) Median % weight gain +21.4%/year (range +15.8-+32.0) Median % ideal body weight +19.9%/year (range -18.7-149.2)	31	p<0.05 for BMI, % weight change and % ideal body weight change per year Also significantly improved health-related quality of life Duration of follow-up 1 year	Very low
Danielsson et al., 2007	<u>BMI SDS:</u> Group 1 (placebo first): -0.68 Group 2 (sibutramine first): -0.72 % body fat -1.9%	 24 21	<u>BMI SDS:</u> Group 1 (placebo first): -0.06 Group 2 (sibutramine first): +0.43 % body fat -0.1%	 24 21	p<0.01 for difference in BMI SDS and % body fat change during each phase of treatment Effect on hypothalamic obesity less pronounced	Moderate

Author(s)	Summary of findings					Quality
	Change in intervention group	No. of patients	Change in control group	No. of patients	Pooled effect	
Ismail et al., 2006	Median BMI SDS -0.7 (males), -0.44 (females)	12	N/A	N/A	Duration of treatment 6-48 months	Very low
Lustig et al., 2003	Weight +1.6 ± 0.6 kg BMI -0.2 ± 0.2 kg/m^2	9	Weight +9.2 ± 1.7 kg BMI +2.2 ± 0.5 kg/m^2	9	Significant differences in mean weight and BMI change Duration of treatment 6 months Note non-significant increases in glucose concentration on OGTT	Low
Fernandes et al., 2002	Weight -14 kg, -4.3 kg and -4.3 kg	3	N/A	N/A	All patients had biochemical hyperthyroidism	Very low
Mason et al., 2002	Mean BMI 32 ± 2.8 kg/m^2 to 31 ± 3.3 kg/m^2	5	N/A	N/A	N/A	Very low
Lustig et al., 1999	Weight -4.8 ± 1.8 kg BMI -2.0 ± 0.7 kg/m^2 Caloric intake -112 cal/day/month	9	N/A	N/A	N/A	Very low

Outcome 3.2.2.5.j: Incidence of sleep disorders

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years who have been treated/ conservatively managed for craniopharyngiomas **I** what is the incidence of daytime somnolence, sleep-wake cycle reversal, obstructive sleep apnoea, narcolepsy **T** at 5, 10, 15, 20 years from diagnosis?	1. craniopharyngioma*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 2. sleep*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 3. (apnoea or apnea or polysomnogra*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 4. 2 or 3 5. 1 and 4 6. exp Craniopharyngioma/ 7. exp Sleep Apnea Syndromes/ or exp Sleep Disorders, Circadian Rhythm/ or exp Sleep/ or exp Sleep Disorders, Intrinsic/ or exp Sleep, REM/ or exp Sleep Apnea, Central/ or exp Sleep Stages/ or exp Sleep Disorders/ or exp Sleep-Wake Transition Disorders/ or exp "Sleep Initiation and Maintenance Disorders"/ or exp Sleep Apnea, Obstructive/ 8. 6 and 7 9. 5 or 8 10. limit 9 to english language	62	31	21	13

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Roemmler-Zehrer et al., 2015(280)	Prospective case-control	Yes – questionnaire-based study	No	Yes – mixed cohort of adults and children (mean age 53 years)	Yes – moderately small cohort of craniopharyngioma patients	No	No	No	No
Joustra et al., 2014(273)	Prospective case-control	Yes – study primarily for pituitary adenomas, craniopharyngioma patients were unmatched to controls	No	Yes – all adult patients	Yes – very small cohort of 8 craniopharyngioma patients	No	No	No	No
Pickering et al., 2014(363)	Prospective case-control	Yes – parametric statistics used for relatively small subcohorts	No	Yes – mixed cohort of adults and children (4/15 <18 years at diagnosis)	Yes – small cohort of craniopharyngioma patients	Yes – patients recruited to this study would possibly have a higher incidence of sleep disorders	No	No	No

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Cohen et al., 2013(281)	Prospective case-control	Yes – parametric statistics used for relatively small subcohorts, all patients were significantly obese (BMI >35 kg/m^2)	No	No	Yes – moderately small cohort of craniopharyngioma patients	No	No	No	No
Manley et al., 2012(277)	Retrospective cohort	Yes – sleep disorders measured by self-report, no control group	No	No	Yes – moderately small cohort	No	No	No	No
Crowley et al., 2011(274)	Prospective case-control	Yes – control group were referrals for exclusion of sleep apnoea (i.e. not healthy)	No	Yes – all adult patients, excluded patients <18 years	Yes – moderately small cohort	No	No	No	No
O'Gorman et al., 2010(272)	Prospective case-control	Yes – parametric statistics used for relatively small subcohorts	No	No	Yes – moderately small cohort	No	No	No	No
van der Klauuw et al., 2008(112)	Prospective case-control	Yes – questionnaire-based study	No	Yes – all adult patients (8/27 diagnosed in childhood)	Yes – moderately small cohort	No	No	No	No
Muller et al., 2006(282)	Prospective case-control/ cohort study	Yes – intervention phase of study was single-arm with no control group	No	No	Yes – small subcohort	Yes – intervention phase of study was single-arm, single-centre with no control group	No	No	No
Ismail et al., 2006(262)	Retrospective cohort	Yes – no control group, daytime somnolence by self-report	No	No	Yes – small cohort of only 12 patients	Yes – small cohort	No	No	No
Snow et al., 2002(275)	Prospective cohort	Yes – very small cohort	No	Yes – mixed cohort of tumours (3/5 craniopharyngiomas)	Yes – very small cohort of 5 patients/ 5 controls	Yes – small cohort	No	No	No
Muller et al., 2002(278)	Prospective case-control	No	No	No	No	No	No	No	No
Palm et al., 1992(276)	Prospective case-control	Yes – small cohort	No	No	Yes – small subcohort of only 10 patients	Yes – small cohort	No	No	No

Author(s)	Summary of findings					Quality
	Frequency/ outcome in craniopharyngioma group	No. of patients	Frequency/ outcome in control group	No. of patients	Pooled effect	
Roemmler-Zehrer et al., 2015	Epworth Sleepiness Scale 9.0 ± 3.9	26	N/A (normal score <10)	N/A	N/A	Very low
Joustra et al., 2014	%REM sleep 18.5 ± 4.7% %awake time 11.6 ± 4.4% Sleep efficiency 87.7 ± 4.4 Total sleep time 439 ± 67 minutes High risk for poor sleep on Berlin Questionnaire 4 Clinical symptom score 4.4 ± 1.9 Epworth Sleepiness Scale 11.4 ± 4.3	8	%REM sleep 25.4 ± 4.4% %awake time 6.6 ± 3.1% Sleep efficiency 92.9 ±3.1 Total sleep time 455 ± 66 minutes High risk for poor sleep on Berlin Questionnaire 0 Clinical symptom score 1.5 ± 1.4 Epworth Sleepiness Scale 4.8 ± 3.2	17 (unmatched)	Sleep efficiency, %REM sleep, %awake time, Epworth Sleepiness Scale and other questionnaire scores all significantly different from controls.	Very low
Pickering et al., 2014	Time of sleep offset 6.7 ± 1.1 Pittsburgh Sleep Quality Index sleep latency 92% Pittsburgh Sleep Quality Index daytime dysfunction 86%	13	Time of sleep offset 8.4 ± 1.3 Pittsburgh Sleep Quality Index sleep latency 54% Pittsburgh Sleep Quality Index daytime dysfunction 50%	13	Significant differences in time of sleep offset, PSQI sleep latency/ daytime dysfunction subscores, and also AUC for cortisol and melatonin secretion	Very low
Cohen et al., 2013	Epworth Sleepiness Scale 10.2 ± 3.6	16	Epworth Sleepiness Scale 6.8 ± 5.3	16	Significant difference in Epworth Sleepiness Scale scores	Very low
Manley et al., 2012	Daytime sleepiness/ sleep disturbance 19 Abnormaly polysomonography 7	28 7	N/A	N/A	No significant association with degree of resection/ radiotherapy	Very low
Crowley et al., 2011	Epworth Sleepiness Scale median 7.5 (IQR 6-10.7) Obstructive sleep apnoea 13 Total sleep time median 7.0 (range 5.6-10.1) hours %sleep efficiency median 85 (range 77-95)%	28	Epworth Sleepiness Scale median 4.0 (IQR 4-8) Obstructive sleep apnoea 14 Total sleep time median 6.2 (range 4.1-6.5) hours %sleep efficiency median 77 (range 55-88)%	23	Significant differences in Epworth Sleepiness Scale, total sleep time and % sleep efficiency (note latter two were better in craniopharyngiomas) 4/5 offered modafinil with improvement with improvement in Epworth Sleepiness Scale 7/9 offered CPAP with improvement	Very low
O'Gorman et al., 2010	Sleep onset latency 19.3 ± 27.8 mins %Sleep stage 2 48.7 ± 9.4% Mean REM SaO_2 89.0 ± 5.1% Mean non-REM SaO_2 88.4 ± 5.6% Minimum SaO_2 86.5 ± 5.9% OAHI 7.5 ± 9.0	15	Sleep-onset latency 31.9 ±23.4 mins %Sleep stage 2 57.0 ± 9.7% Mean REM SaO_2 94.2 ± 2.3% Mean non-REM SaO_2 94.3 ± 1.5% Minimum SaO_2 93.6 ± 2.1% OAHI 1.5 ± 1.5	15	All significant differences Correlations with leptin, insulin sensitivity, adiponectin, and IL-6 concentrations	Very low
van der Klauuw et al., 2008	Epworth Sleepiness Scale 7.7 ± 4.1 (33% >10) Snoring 72% Apnoeas 29%	27	Epworth Sleepiness Scale 4.8 ± 3.4 (8% >10) Snoring 74% Apnoeas 10%	38	Significant differences on Epworth Sleepiness Scale but not Munchener Chronotype Questionnaire No association with type of surgical resection (transsphenoidal vs. transcranial) or radiotherapy	Very low

Author(s)	Summary of findings					Quality
	Frequency/ outcome in craniopharyngioma group	No. of patients	Frequency/ outcome in control group	No. of patients	Pooled effect	
Muller et al., 2006	Epworth Sleepiness Scale: BMI <4 SDS median 4.5 (range 0-19) BMI >4 SDS median 10.0 (range 1-19)	 49 30	Epworth Sleepiness Scale: BMI <4 SDS median 2 (range 0-5) BMI >4 SDS median 4 (range 1-6)	 16 14	Significant differences in Epworth Sleepiness Scale in severely obese vs. non-severely obese craniopharyngioma patients No significant differences in salivary melatonin concentrations, but significant correlation with Epworth score Epworth score improved in 10 patients with melatonin treatment	Very low
Ismail et al., 2006	N/A	N/A	N/A	N/A	8/8 with daytime somnolence improved with dexamphetamine	Very low
Snow et al., 2002	Epworth Sleepiness Scale 15.2 ± 2.8 Stage 3-4 sleep 143 ± 43.7 minutes Multiple sleep latency test sleep latency 10.3 ± 5.3 minutes	5	Epworth Sleepiness Scale 5.0 ± 2.0 Stage 3-4 sleep 79.5 ± 30.7 minutes Multiple sleep latency test sleep latency 26.2 ± 1.1 minutes	5	All significant differences No significant differences in blood or CSF orexin levels	Very low
Muller et al., 2002	Epworth Sleepiness Scale: BMI <2 SDS median 3 (range 0-19) BMI 2-4 SDS median 7 (range 1-17) BMI >4 SDS median 10.0 (range 1-19)	79	Epworth Sleepiness Scale: BMI <2 SDS median 2 (range 0-5) BMI 2-4 SDS median 3 (range 0-5) BMI >4 SDS median 4 (range 1-6)	30	Significant difference in Epworth scores for craniopharyngioma patients with BMI >4 SDS compared to controls No significant differences in salivary melatonin concentrations, but negative correlations with BMI and Epworth score	Low
Palm et al., 1992	No whole cohort averages presented	10	N/A	18	Total sleep time, % REM sleep and sleep efficiency significantly lower and frequency of wakenings and time awake significantly higher in craniopharyngioma patients	Very low

Outcome 3.2.2.5.k: Incidence of cognitive/neuropsychological deficits

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years who have been treated/ conservatively managed for craniopharyngiomas **I** what is the incidence of cognitive deficits, psychiatric disorders, children requiring special educational need support, adults not achieving fully independent living **T** at 5, 10, 15, 20 years from diagnosis?	1. craniopharyngioma*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 2. (cognit* or behav* or psych* or disability or special needs or independen* or autis*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 3. 1 and 2 4. exp Craniopharyngioma/ 5. exp Cognition Disorders/ or exp Cognition/ 6. exp Child Behavior Disorders/ 7. exp Psychiatry/ or exp Mental Disorders/ 8. exp Intellectual Disability/ 9. exp "Activities of Daily Living"/ 10. exp Disabled Persons/ or exp Disabled Children/ 11. exp Independent Living/ 12. exp Autistic Disorder/ or exp Developmental Disabilities/ 13. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 14. 4 and 13 15. 3 or 14 16. limit 15 to (english language and "all child (0 to 18 years)")	289	71	53	37 (however, note none provided data on best practice for monitoring neuropsychological outcomes therefore Delphi consensus)

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Yano et al., 2016(298)	Prospective cohort	Yes – single centre	No	No	Yes – relatively small cohort of 26 patients	Yes – single centre	No	No	No
Sterkenburg et al., 2015(34)	Prospective case-control	No	No	No	No	No	No	Yes – patients from multicentre, multi-country HIT-ENDO registry	No
Gerganov et al., 2014(305)	Retrospective cohort	Yes – single centre, all patients undergoing one specific surgical procedure	No	Yes – mixed cohort of adults and children (5/16 <19 years)	Yes – small cohort of 16 patients	Yes – single centre	No	No	No
Rath et al., 2013(293)	Retrospective cohort	Yes – single centre, some deficits by self-report	No	No	Yes – very small cohort of 10 patients (only 2 with formal testing)	Yes – single centre	No	No	No

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Netson et al., 2013(316)	Prospective cohort	Yes – only patients receiving radiotherapy included	No	No	No	Yes – single centre, all patients received radiotherapy	No	No	No
Laffond et al., 2013(309)	Retrospective cohort	Yes – only patients receiving proton beam therapy included	No	No	Yes – relatively small cohort of 29 patients	Yes – single centre	No	No	No
Leng et al., 2012(306)	Retrospective cohort	Yes – single centre, all patients undergoing one specific surgical procedure, outcomes by self-report	No	Yes – mixed cohort of adults and children (mean 43.6 years)	Yes – relatively small cohort of 26 patients	Yes – single centre	No	No	No
Ondruch et al., 2011(290)	Prospective cohort	No	No	No	Yes – relatively small cohort of 27 patients	Yes – low return rate of responses	No	No	No
Crom et al., 2010(286)	Retrospective cohort	Yes – formal testing not performed systematically	No	No	No	No	No	No	No
Elliott & Wisoff, 2010(131)	Retrospective cohort	Yes – formal testing not performed systematically (most data "unavailable")	No	No	Yes – relatively small cohort of 26 patients	Yes – only giant craniopharyngiomas included	No	No	No
Elliott et al., 2010(287)	Retrospective cohort	Yes – single centre, all underwent attempted radical resection by single surgeon, no formal neuropsychological assessment	No	No	No	Yes – single centre, single surgeon	No	No	No
Kawamata et al., 2010(317)	Retrospective cohort	Yes – single centre, unclear methods of assessment	No	Yes – mixed cohort of adults and children at diagnosis	No	Yes – single centre	No	No	No
Jang et al., 2009(289)	Retrospective cohort	Yes – unclear methods of assessment	No	No	Yes – very small cohort of 7 patients	Yes – single centre	No	No	No
Dolson et al., 2009(315)	Prospective cohort	No	No	No	Yes – moderately small cohort of 27 patients	Yes – single centre, all patients had radiotherapy	No	No	No

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Derrey et al., 2008(229)	Retrospective cohort	Yes – unclear methods of assessment	No	Yes – mixed cohort of adults and children (11/42 <16 years)	No	Yes – single centre, only patients undergoing ^{186}Re intracavitary irradiation	No	No	No
Puget et al., 2007(26)	Retrospective/ prospective cohort	Yes – unclear if assessment was systematically performed	No	No	No	Yes – single centre	No	No	No
Shi et al., 2006(364)	Retrospective cohort	Yes – unclear methods of assessment	No	Yes – mixed cohort of adults and children (58/284 <15 years)	No	Yes – single centre	No	No	No
Pedreira et al., 2006(291)	Prospective case-control	Yes – incomplete data on controls	No	No	Yes – small cohort of 18 patients	Yes – single centre, poor response rate (39%)	No	No	No
Waber et al., 2006(304)	Prospective cohort	No	No	No	Yes – small cohort of 10 patients	No	No	No	No
Sands et al., 2005(294)	Prospective cohort	No	No	No	Yes – relatively small cohort of 29 patients	Yes – single centre, moderate response rate (57%)	No	No	No
Minamida et al., 2005(301)	Retrospective cohort	No	No	Yes – mixed cohort of adults and children (8/37 <16 years)	Yes – relatively small cohort of 37 patients	Yes – single centre, patients who had radiotherapy excluded	No	No	No
Pierre-Kahn et al., 2005(292)	Prospective cohort	No	No	No	Yes – small cohort of 14 patients	Yes – single centre, all patients had radical resection	No	No	No
Thompson et al., 2005(296)	Retrospective cohort	Yes - unclear validity of scoring system	No	No	No	Yes – single centre	No	No	No
Kendall-Taylor et al., 2005(297)	Retrospective cohort (using pharmacovigilance database)	No	No	No (note comparison made between adult and childhood craniopharyngioma)	No	Yes – only included patients with treated GH deficiency	No	Yes – multicentre, multi-country database	No

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Karavitaki et al., 2005(24)	Retrospective cohort	Yes – unclear methods of assessment	No	Yes – mixed cohort of adults and children (42/121 <16 years), outcomes for children not separated	No	Yes – single centre	No	No	No
Poretti et al., 2004(279)	Prospective cohort	No	No	No	Yes – relatively small cohort of 21 patients	Yes – single centre, overall radical resection as treatment strategy	No	No	No
Jackson et al., 2003(288)	Prospective cohort	Yes – only qualitative outcomes reported	No	No	Yes – relatively small cohort of 13 families	Yes – single centre	No	No	No
Kalapurakal et al., 2003(271)	Retrospective cohort	Yes – assessments not systematically performed	No	No	Yes – relatively small cohort of 25 patients	Yes – single centre	No	No	No
Ulfarsson et al., 2002(214)	Retrospective cohort	Yes – unclear methods of assessment	No	Yes – mixed cohort of adults and children (11/21 <15 years)	Yes – relatively small cohort of 21 patients	Yes – single centre, only patients undergoing radiosurgery included	No	No	No
Merchant et al., 2002(25)	Retrospective cohort	No	No	No	Yes – relatively small cohort of 30 patients	Yes – single centre	No	No	No
Carpentieri et al., 2001(300)	Prospective cohort	No	No	No	Yes – relatively small cohort of 16 patients	Yes – single centre, all patients only had surgery	No	No	No
Duff et al., 2000(299)	Retrospective cohort	Yes – unclear methods of assessment	No	Yes – mixed cohort of adults and children (32/121 <16 years)	No	Yes – single centre	No	No	No
Fahlbusch et al., 1999(15)	Retrospective cohort	Yes – unclear methods of assessment	No	Yes – mixed cohort of adults and children (30/148 <16 years)	No	Yes – single centre	No	No	No
Donnet et al., 1999(307)	?Prospective cohort	No	No	Yes – mixed cohort of adults and children	Yes – relatively small cohort of 22 patients	Yes – single centre	No	No	No
Riva et al., 1998(310)	Prospective cohort	No	No	No	Yes – relatively small cohort of 12 patients	Yes – single centre	No	No	No

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Anderson et al., 1997(285)	Retrospective cohort	Yes – unclear methods of assessment	No	No	Yes – relatively small cohort of 20 patients	Yes – single centre	No	No	No
Villani et al., 1997(314)	Retrospective cohort	Yes – unclear methods of assessment	No	No	Yes – relatively small cohort of 27 patients	Yes – single centre, overall aim was for radical resection	No	No	No

Author(s)	Summary of findings					Quality
	Frequency/ outcome in craniopharyngioma group	No. of patients	Frequency/ outcome in control group	No. of patients	Pooled effect	
Yano et al., 2016	Lower mental component summary of SF-36/ CHQ-PF50 compared to national standards	26	N/A	N/A	N/A	Very low
Sterkenburg et al., 2015	Married 7 Children/ pregnancy 1 Friends 23 Professional education 30 Employed 24 Driver's licence 21 Psychological treatment 12	35	Married 12 Children/ pregnancy 11 Friends 24 Professional education 28 Employed 20 Driver's licence 29 Psychological treatment 1	30	Significant differences in "children/pregnancy", "driver's licence", and "psychological treatment" Hypothalamic involvement significantly associated with "married" and "driver's licence"	Moderate
Gerganov et al., 2014	Transient psychosis 1 Short-term memory loss 3	16	N/A	N/A	N/A	Very low
Rath et al, 2013	Neuropsychological testing (for learning difficulties) 2 Poor school performance 2	10	N/A	N/A	N/A	Very low
Netson et al., 2013	Decline in Communication and Socialisation scores on Vineland Adaptive Behaviour Scale	62	N/A	N/A	N/A	Very low
Laffond et al., 2013	Psychological/ psychiatric follow-up 11 Anxiety/ depression 2 Depression on MDI-C 11 Elevated BRIEF sub-scales 24-38% Repeating school year 10 Special needs schooling 3 Graduated high school 2	29 5	N/A	N/A	N/A	Very low
Leng et al., 2012	Memory loss 3 Returned to work/ school 69%	26 18	N/A	N/A	N/A	Very low

Author(s)	Summary of findings					Quality
	Frequency/ outcome in craniopharyngioma group	No. of patients	Frequency/ outcome in control group	No. of patients	Pooled effect	
Ondruch et al., 2011	Mean IQ 103 (range 79-129) Rey-Osterrieth Complex Figure Test 50-60% below average No significant difference in individual subject scores CBCL anxiety/ depression 11% CBCL social problems 30% CBCL withdrawal/ depression 11%	27	N/A	N/A	N/A	Very low
Crom et al., 2010	Neurocognitive delay 10 Individual education plan 10 College graduate 2 Postgraduate degree 1 Psychological problems 15 Communication disorder 5	51	N/A	N/A	N/A	Very low
Elliott & Wisoff, 2010	Memory deficits 4 Repeated school year 7	26	N/A	N/A	N/A	Very low
Elliott et al., 2010	IQ <80 4 Significant disability needing assistance 4 College attendance 35	86 48	N/A	N/A	N/A	Very low
Kawamata et al., 2010	Cognitive impairment 15	55	N/A	N/A	Multiple interventions and radiotherapy associated with increased cognitive impairment	Very low
Jang et al., 2009	Cognitive impairment/ learning disability 7 Neuropsychological and behavioural disorders 3	7	N/A	N/A	N/A	Very low
Dolson et al., 2009	N/A	27	N/A	N/A	Worsening CBCL scores over time with CSF shunting procedures, improved scores with no central DI, Ommaya reservoir insertion	Very low
Derrey et al., 2008	Worsening memory 1	42	N/A	N/A	N/A	Very low
Puget et al., 2007	<u>Retrospective cohort:</u> Memory disturbance 11 Special educational needs schooling 2 Major behavioural disorder 5	107 45	N/A	N/A	Higher tumour grade associated with behavioural disturbances	Very low
Shi et al., 2006	Severe disability 1 Assistance for activities of daily living 9	284	N/A	N/A	N/A	Very low

Author(s)	Summary of findings					Quality
	Frequency/ outcome in craniopharyngioma group	No. of patients	Frequency/ outcome in control group	No. of patients	Pooled effect	
Pedreira et al., 2006	Psychological general well-being score 69.4 ± 18.7 Children 0 Assistance for activities of daily living 5 Reduced IQ 8 Reduced Vineland Behaviour Adaptive Scale 9 Significant Revised Children's Manifest Anxiety Scale Significant Short Mood & Feeling's Questionnaire Score (depression) 2 Graduate education 5	18 12 12 12 10 11	Psychological general well-being score 75.3 ± 16.1 No other clear data on controls	18	N/A	Very low
Waber et al., 2006	Low IQ 1 Low coding/ Digit Symbol IQ 5 Poor calculation 1 Poor verbal learning 2 Poor Complex Figure Test 4 Low spatial working memory 3 Low behavioural memory 7 Everyday cognitive problems 9 Depression 5	10	N/A	N/A	N/A	Very low
Sands et al., 2005	Mental health QoL (SF-36) 41.6 ± 16.4 (low average) Psychosocial QoL (CHQ-PF50) 46.5 ± 11.9 (average) Social emotional/ behavioural functioning (CBCL) 52.3 ± 13.4 (average) Internalising problems (CBCL) 61.7 ±11.9 (borderline significant)	29	N/A	N/A	Retrochiasmatic lesions associated with lower psychosocial QoL and have greater social-emotional and behavioural problems	Very low
Minamida et al., 2005	IQ 101.1 (range 58-124) with slight reduction Karnofsky Performance Score 87.1 (range 70-90), no change	37	N/A	N/A	N/A	Very low
Pierre-Kahn et al., 2005	Conduct disorders 4 Depressive symptoms 9 School difficulties 4 Mean Children's Global Assessment Scale 59.3 IQs stable	14	N/A	N/A	N/A	Very low
Thompson et al., 2005	Moderate-severe learning difficulties/ special educational needs 10	48	N/A	N/A	N/A	Very low

Author(s)	Summary of findings					Quality
	Frequency/ outcome in craniopharyngioma group	No. of patients	Frequency/ outcome in control group	No. of patients	Pooled effect	
Kendall-Taylor et al., 2005	AGHDA score 9.6 ± 6.8 Married 14.6% Unemployed 8.9%	152	N/A	N/A	Worse AGHDA scores for adult-onset craniopharyngiomas, both worse than general population	Low
Karavitaki et al., 2005	Complete dependency for activities of daily living 11% Unable to work in previous occupation 48% Underperformance at school 28% Depression/ mood disorders 33%	109 61 27 103	N/A	N/A	N/A	Very low
Poretti et al., 2004	Significant Youth Self Report behavioural score 5 Significant CBCL score 8	12	N/A	N/A	N/A	Very low
Jackson et al., 2003	Only qualitative outcomes with no thematic analysis provided	13	N/A	N/A	N/A	Very low
Kalapurakal et al., 2003	Neuropsychological/ behavioural disorders 5 Neurocognitive disorders/ learning difficulties 3	25	N/A	N/A	N/A	Very low
Ulfarsson et al., 2002	Full recovery to independent living 7	7	N/A	N/A	N/A	Very low
Merchant et al., 2002	Full scale IQ decline 7 Verbal IQ decline 3 Performance IQ decline 3 Impaired QoL on Health Utilities Index 23	23 26 20 29	N/A	N/A	Decline in IQ associated with relapse> surgery> STR + radiotherapy Slightly higher QoL with STR+ radiotherapy vs. surgery alone	Very low
Carpentieri et al., 2001	Reduced IQ 0 Impaired Boston Naming Test 31.3% Impaired Sentence Memory 6.3% Impaired Story Memory (delayed recall) 37.5% Impaired Story Memory (recognition) 6.3% Impaired Visual Motor Integration 6.3% Impaired Rey-Osterreith Complex Figure Test 6.3-86.7%	16	N/A	N/A	N/A	Very low
Duff et al., 2000	Underperformance at school 4 Unemployed 15 Psychological/ emotional treatment 27	48 100 121	N/A	N/A	N/A	Very low
Fahlbusch et al., 1999	Independence without impairment 117	148	N/A	N/A	N/A	Very low

Author(s)	Summary of findings					Quality
	Frequency/ outcome in craniopharyngioma group	No. of patients	Frequency/ outcome in control group	No. of patients	Pooled effect	
Donnet et al., 1999	Episodic memory deficit 4 Frontal dysfunction 5 Learning & retention defects 4 Impaired conceptual functions 1 Impaired visuoconstructive abilities 5 Return to work 12	22 19	N/A	N/A	N/A	Very low
Riva et al., 1998	Inability to withstand frustration 10 Fits of anger 5 Emotional lability 3 Frontal dysfunction 5 Impaired IQ 0 Impaired verbal/ spatial memory 0 Impaired attention/ motor ability 4 Decreased academic performance 3	12	N/A	N/A	N/A	Very low
Anderson et al., 1997	Moderate/ severe neurobehavioural impairment 12 Severe cognitive dysfunction 5	20	N/A	N/A	No association between degree of resection and outcome	Very low
Villani et al., 1997	Psychosocial disturbance 59% Moderate impairment of function 4	22	N/A	N/A	N/A	Very low

Outcome 3.2.2.6.a-c: Management of recurrence after GTR/ STR

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years who have had primary complete resection of a craniopharyngioma with a relapse/ recurrence **I** does radiotherapy with further complete or incomplete resection **C** compared to radiotherapy only without further surgery **O** improve overall and progression-free survival?	1. exp Craniopharyngioma/ or craniopharyngioma*.mp. 2. limit 1 to "all child (0 to 18 years)" 3. radiotherapy.mp. or exp Radiotherapy/ 4. relapse.mp. or Recurrence/ 5. recurrence.mp. 6. 4 or 5 7. 2 and 3 and 6 8. (surgery or resection or incomplete or complete).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 9. 7 and 8	202	104	28	10

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Steno et al., 2014(321)	Retrospective cohort	Yes – unable to calculate events post-treatment for recurrence	No	Yes – mixed cohort of adults and children (38/101 <18 years)	No	Yes – single centre	No	No	No
Mortini et al., 2011(320)	Retrospective cohort	Yes – unable to determine degree of primary resection prior to recurrence in individual patients	No	Yes – mixed cohort of adults and children (34/112 <18 years)	Yes – relatively small subcohort (26) who had recurrence	Yes - single centre	No	No	No
Liubinas et al., 2011(319)	Retrospective cohort	Yes – unable to determine degree of primary resection in relation to treatment for recurrence and outcomes for individual patients	No	Yes – mixed cohort of adults and children (mean age 51 years (range 17-72))	Yes – relatively small subcohort (28) who had GTR as primary treatment	Yes – single centre	No	No	No
Vinchon & Dhellemmes et al., 2008(322)	Retrospective cohort	Yes – unable to determined degree of primary resection in relation to outcomes and also use of radiotherapy in recurrence	No	No	Yes – relatively small cohort of 20 children, even smaller subcohort (7/20) post-GTR as primary treatment	Yes – single centre	No	No	No

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Minamida et al., 2005(301)	Retrospective cohort	Yes – radiotherapy not considered in recurrence, unclear outcomes by degree of resection fo recurrence	No	No	Yes – small cohort of 11 patients , even smaller subcohort (5/11) post-GTR as primary treatment	Yes – single centre	No	No	No
Lena et al., 2005(225)	Retrospective cohort	Yes – unclear outcomes by treatment modality for recurrence	No	No	Yes – relatively small cohort of 16 patients, even smaller subcohort (7/16) with GTR as primary treatment	Yes – single centre	No	No	No
Caldarelli et al., 2005(22)	Retrospective cohort	Yes – no outcomes reported for treatments for recurrence	No	No	Yes – small cohort of 9 patients, even smaller subcohort (3/9) with GTR as primary treatment	Yes – single centre	No	No	No
Stripp et al., 2004(141)	Retrospective cohort	Yes – difficult to separate outcomes by treatment modality for recurrence	No	No	No	Yes – single centre	No	No	No
Barua et al., 2003(323)	Retrospective cohort	No	No	Yes – mixed cohort of adults and children (16/61 of original cohort <16 years)	Yes – relatively small cohort of 24 patients	Yes – single centre	No	No	No
Kalapurakal et al., 2000(318)	Retrospective cohort	Yes – did not include patients who had primary radiotherapy	No	No	Yes – relatively small cohort of 14 patients	Yes – single centre	No	No	No

Author(s)	Summary of findings					Quality
	No. of events in radiotherapy group	No. of patients	No. of events in non-radiotherapy group	No. of patients	Pooled effect	
Steno et al., 2014	N/A	N/A	N/A	N/A	Unable to calculate re-recurrence rate after treatment for recurrence but repeated surgery reduced chance of GTR	Very low
Mortini et al., 2011	<u>Re-recurrence:</u> Radiotherapy alone 2	5	<u>Re-recurrence:</u> Surgery alone 5	10	N/A	Very low

Author(s)	Summary of findings					Quality
	No. of events in radiotherapy group	No. of patients	No. of events in non-radiotherapy group	No. of patients	Pooled effect	
Liubinas et al., 2011	N/A (none treated with radiotherapy for recurrence)	N/A	Re-recurrence: GTR alone 3 STR alone 3 Visual deterioration: GTR alone 3 STR alone 2 New central DI: GTR alone 5 STR alone 2	 38 16 38 16 38 16	N/A	Very low
Vinchon & Dhellemmes, 2008	10-year PFS: Radiotherapy outcome data not presented	3	10-year PFS: GTR 55.6% STR 34.3%	 6 14	Non-significant difference between PFS post-GTR vs. STR for recurrence No significant differences between functional outcome, BMI or IQ, but repeated surgery associated with poor functional outcomes	Very low
Minamida et al., 2005	N/A (radiotherapy not used in recurrence)	N/A	N/A	N/A	Unclear outcomes by degree of resection for recurrence	Very low
Lena et al., 2005	N/A	N/A	N/A	N/A	Unclear outcomes by treatment modality for recurrence	Very low
Caldarelli et al., 2005	N/A	N/A	N/A	N/A	Unclear outcomes by treatment modality for recurrence	Very low
Stripp et al., 2004	N/A	N/A	N/A	N/A	No significant difference in PFS for salvage vs. adjuvant radiotherapy	Very low
Barua et al., 2003	Re-recurrence: STR + radiotherapy 2 SRS 1 5-year post-recurrence PFS: STR + radiotherapy 80% SRS 83.3% Visual deterioration: STR + radiotherapy 0 SRS 0 Poor functional status: STR + radiotherapy 3 SRS 1	 7 7 7 7 7 7	Re-recurrence: GTR alone 0 STR alone 10 5-year post-recurrence PFS: GTR alone 50% STR alone 16% Visual deterioration: GTR alone 1 STR alone 2 Poor functional status: GTR alone 0 STR alone 7	 4 19 4 19 4 19	Significantly lower 5-year post-recurrence PFS for surgery alone (GTR/ STR) vs. radiotherapy (conventional/ SRS) +/- surgery	Very low
Kalapurakal et al., 2000	5-year post-recurrence PFS: Radiotherapy alone 100% 15-year overall PFS: Radiotherapy +/- surgery 83%	 5	5-year post-recurrence PFS: Surgery alone 0% 15-year overall PFS: Surgery alone 0%	 7	N/A	Very low

Outcome 3.2.2.6.d: Efficacy/ toxicity of second course radiotherapy

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years who have had radiotherapy for craniopharyngiomas **I** does further radiotherapy **C** compared to other therapeutic modalities (e.g. repeat surgery, intracystic therapies, radiosurgery) **O** improve overall and progression-free survival?	1. exp Craniopharyngioma/ or craniopharyngioma*.mp. 2. limit 1 to "all child (0 to 18 years)" 3. radiotherapy.mp. or exp Radiotherapy/ 4. relapse.mp. or Recurrence/ 5. recurrence.mp. 6. 4 or 5 7. 2 and 3 and 6 8. (repeat or 2nd or second or further).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 9. 7 and 8	56	40	17	0 (therefore Delphi consensus)

Outcome 3.2.2.6.e: Efficacy of SRS for recurrence

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years who have had a relapse or progression of a craniopharyngioma **I** does stereotactic radiosurgery **C** compared to further complete/ incomplete resection/ conventional radiotherapy alone/ conventional radiotherapy + further complete/ incomplete resection **O** lead to equivalent overall and progression-free survival, reduced cognitive impairment, reduced visual impairment, reduced hypothalamo-pituitary dysfunction?	1. exp *Craniopharyngioma/ or craniopharyngioma*.mp. 2. limit 1 to "all child (0 to 18 years)" 3. relapse.mp. or exp *Recurrence/ 4. recurrence.mp. 5. progression.mp. or exp *Disease Progression/ 6. 3 or 4 or 5 7. stereotactic radiosurgery.mp. or exp *Radiosurgery/ 8. 2 and 6 9. 7 and 8 10. neurosurgery.mp. or exp *Neurosurgery/ 11. radiotherapy.mp. or exp *Radiotherapy/ 12. 10 or 11 13. 9 and 12	47	37	17	8

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Jeon et al., 2011(327)	Retrospective cohort	Yes – single centre, no multivariate analysis incorporating timing of radiotherapy	No	Yes – mixed cohort of adults and children (median 33.6 years), mixed cohort of tumours (24 recurrent and 26 residual tumours)	Yes – relatively small subcohort receiving SRS (13/50)	Yes – single centre	No	No	No
Xu et al., 2011(328)	Retrospective cohort	Yes – no comparison to other treatments	No	Yes – mixed cohort of adults and children (17/37 <21 years), mixed cohort of tumours (4 primary, 33 recurrent)	No	Yes – single centre	No	No	No
Niranjan et al., 2010(206)	Retrospective cohort	Yes – single centre, no comparison to other treatments	No	Yes – mixed cohort of adults and children (but median age 23.5 years), mixed cohort of tumours (3 primary, 43 recurrent)	No	Yes – single centre	No	No	No

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Gopalan et al., 2008(326)	Non-systematic review of cohort studies	Yes – none of included studies contained a comparison group	No	Yes – mixed cohort studies of adults and children included (only 3/10 studies were paediatric), studies included primary and recurrent tumours (63% recurrent)	No	No	No	No	No
Kobayashi et al., 2005(212)	Retrospective cohort	Yes – single centre, no comparison to other treatments	No	Yes – mixed cohort of adults and children (38/98 <15 years), mixed cohort of tumours (unclear proportion)	No	Yes – single centre	No	No	No
Barua et al., 2003(323)	Retrospective cohort	No	No	Yes – mixed cohort of adults and children (16/61 of original cohort <16 years)	Yes – small subcohort receiving SRS (7/24)	Yes – single centre	No	No	No
Chiou et al., 2001(215)	Retrospective cohort	Yes – single centre, no comparison to other treatments	No	Yes – mixed cohort of adults and children (8/10 <19 years)	Yes – small cohort of 10 patients	Yes – single centre	No	No	No
Mokry, 1999(213)	Retrospective cohort	Yes – single centre, no comparison to other treatments	No	Yes – mixed cohort of adults and children (8/23 <15 years)	Yes – relatively small cohort of 23 patients	Yes – single centre	No	No	No

Author(s)	Summary of findings					Quality
	No. of events in SRS group	No. of patients	No. of events in non-SRS group	No. of patients	Pooled effect	
Jeon et al., 2011	Mean PFS: SRS 1907 days (1261-2552)	13	Mean PFS: Conventional radiotherapy 2816 days (2070-3561)	37	No significant difference in PFS between SRS and conventional radiotherapy	Very low
Xu et al., 2011	5-year PFS 67.0% Progression 4 5-year OS 75.6% Deaths 9 Visual deterioration 3 New panhypopituitarism 1	37	N/A (no comparison to conventional radiotherapy/ other treatments)	N/A	Multivariate predictors of better PFS: Absence of visual field defect at SRS HR 0.011 (0.0005-0.258) SRS volume <1.6 cm^3 HR 0.13 (0.023-0.744) Marginal dose >14.5 Gy HR 0.041 (0.002-0.688)	Very low

Author(s)	Summary of findings					Quality
	No. of events in SRS group	No. of patients	No. of events in non-SRS group	No. of patients	Pooled effect	
NIranjan et al., 2010	5-year PFS 67.8% Progression 20 Deaths 5 Visual deterioration 7 New panhypopituitarism 1	46	N/A (no comparison to conventional radiotherapy/ other treatments	N/A	Univariate predictors of better PFS: complete SRS coverage of tumours, previous radiotherapy/ [22]P	Very low
Gopalan et al., 2008	Progression 25% (range 0-67%) Local control 75% (range 36-100%)	N/A	N/A	N/A	N/A (no meta-analysis)	Very low
Kobayashi et al., 2005	Progression 20 Deaths 16	98	N/A (no comparison to conventional radiotherapy/ other treatments)	N/A	N/A	Very low
Barua et al., 2003	<u>Re-recurrence:</u> SRS 1 <u>5-year post-recurrence PFS:</u> SRS 83.3% <u>Visual deterioration:</u> SRS 0 <u>Poor functional status:</u> SRS 1	 7 7 7	<u>Re-recurrence:</u> GTR alone 0 STR alone 10 STR + radiotherapy 2 <u>5-year post-recurrence PFS:</u> GTR alone 50% STR alone 16% STR + radiotherapy 80% <u>Visual deterioration:</u> GTR alone 1 STR alone 2 STR + radiotherapy 0 <u>Poor functional status:</u> GTR alone 0 STR alone 7 STR + radiotherapy 3	 4 19 7 4 19 7 4 19 7	Significantly lower 5-year post-recurrence PFS STR alone vs. radiotherapy (conventional/ SRS) +/- surgery	Very low
Chiou et al., 2001	Progression/ recurrence 2 Deaths 0 Visual deterioration 1 Endocrine deterioration 0	10	N/A (no comparison to conventional radiotherapy/ other treatments)	N/A	N/A	Very low
Mokry 1999	Progression 7 Deaths 2	23	N/A (no comparison to conventional radiotherapy/ other treatments)	N/A	Smaller mean tumour volume associated with better responses	Very low

Outcome 3.2.2.6.f: Efficacy of intracystic therapies for recurrent cystic craniopharyngiomas

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years who have had a relapse or progression of a cystic craniopharyngioma **I** does primary intracystic instillation of bleomycin, IFNα, radioisotopes **C** compared to resection/ cyst aspiration and drainage/ radiotherapy or conservative management **O** result in equivalent overall and progression-free survival, reduced cognitive impairment, reduced visual impairment, reduced hypothalamo-pituitary dysfunction?	1. exp *Craniopharyngioma/ or craniopharyngioma*.mp. 2. limit 1 to "all child (0 to 18 years)" 3. relapse.mp. or exp *Recurrence/ 4. recurrence.mp. 5. progression.mp. or exp *Disease Progression/ 6. 3 or 4 or 5 7. 2 and 6 8. (intracystic or cystic).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 9. (bleomycin or interferon or isotopes or yttrium or phosphorus or 32P or 90Y).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 10. 7 and 8 11. exp *Yttrium Radioisotopes/ or exp *Yttrium/ or exp *Yttrium Isotopes/ 12. exp *Phosphorus Isotopes/ or exp *Phosphorus/ or exp *Phosphorus Radioisotopes/ 13. exp *Radioisotopes/ 14. exp *Bleomycin/ 15. exp *Interferon-alpha/ 16. 9 or 11 or 12 or 13 or 14 or 15 17. 10 and 16	43	37	15	9

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Goldman et al., 2020(332)	Prospective cohort	Yes – no comparison to conventional treatments	No	No	Yes – relatively small cohort of 18 patients	No	No	No	No
Maarouf et al., 2016(330)	Retrospective cohort	Yes – no comparison to conventional treatments	No	Yes – mixed cohort of tumours (6 primary, 11 recurrent)	Yes – relatively small cohort of 17 patients	Yes – single centre	No	No	No
Julow et al., 2007(329)	Retrospective cohort	Yes – no comparison to conventional treatments, inadequate discussion about subsequent progressions	No	Yes – mixed cohort of adults and children (27% children)	No	Yes – single centre	No	No	No

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Lena et al., 2005(225)	Retrospective cohort	Yes – inadequate discussion about subsequent progressions post-recurrence	No	No	Yes – only 2/53 children treated with intracystic bleomycin for recurrent tumours	Yes – single centre	No	No	No
Mottolese et al., 2005(226)	Retrospective cohort	Yes – unable to separate outcome data between primary and recurrent tumours	No	Yes – mixed cohort of primary and recurrent tumours	Yes – only 6/60 children treated with intracystic bleomycin for recurrent tumours	Yes – single centre	No	No	No
Hukin et al., 2005(224)	Retrospective cohort	Yes – unable to separate outcome data for conventional treatments	No	No	Yes – only 3/29 children treated with bleomycin for recurrent tumours	Yes – single centre	No	No	No
Hasegawa et al., 2004(230)	Retrospective cohort	Yes – no comparison to conventional treatments, unable to separate outcome data between primary and recurrent tumours	No	Yes – mixed cohort of adults and children (15/49 <16 years)	Yes – relatively small cohort (24/49) treated with ^{32}P for recurrent tumours	Yes – single centre	No	No	No
Mottolese et al., 2001(331)	Retrospective cohort	Yes – no comparison to conventional treatments	No	Yes – mixed cohort of adults and children (20/24 children)	Yes – relatively small cohort (8/24) treated with bleomycin for recurrent tumours	Yes – single centre	No	No	No
Blackburn et al., 1999(228)	Case series	Yes – no comparison to conventional treatments	No	Yes – mainly adult patients (2/6 <16 years)	Yes – case series of only 6 patients	Yes – single centre case series	No	No	No

Author(s)	Summary of findings					Quality
	No. of events in intracystic therapy group	No. of patients	No. of events in non-intracystic therapy group	No. of patients	Pooled effect	
Goldman et al., 2020	Previous surgery: partial response 2, 2-year PFS 27.8% Previous radiotherapy: any response 0, 2-year PFS 34.1%	7 11	N/A (no comparison to conventional treatments)	N/A	N/A	Very low

Author(s)	Summary of findings					Quality
	No. of events in intracystic therapy group	No. of patients	No. of events in non-intracystic therapy group	No. of patients	Pooled effect	
Maarouf et al., 2016	Progression 3 5-year PFS (in-field) 81% 5-year PFS (overall) 52% Cyst volume reduction median 24.8% (range 0-40) Visual deterioration 1 Endocrine deterioration 4	17	N/A (no comparison to conventional treatments)	N/A	N/A	Very low
Julow et al., 2007	Cyst volume reduction mean 88.3% 29-year OS 0% Visual deterioration 3	60 52	N/A (no comparison to conventional treatments)	N/A	N/A	Very low
Lena et al., 2005	Progression 0	2	<u>Progression:</u> Radiotherapy alone 0 SRS N/A Surgery alone N/A	 3 5 6	N/A	Very low
Mottolese et al., 2005	N/A	N/A	N/A	N/A	Unable to separate outcome data between primary and recurrent tumours	Very low
Hukin et al., 2005	Progression 2	3	N/A	N/A	Unable to separate outcomes for conventional treatments	Very low
Hasegawa et al., 2004	Progression 5 10-year PFS 70%	49	N/A (no comparison to conventional treatments)	N/A	N/A	Very low
Mottolese et al., 2001	Cyst reduction 8 Progression 0	8	N/A (no comparison to conventional treatments)	N/A	N/A	Very low
Blackburn et al., 1999	Progression 4	6	N/A (no comparison to conventional treatments)	N/A	N/A	Very low

Outcome 3.2.2.6.g: Efficacy of systemic IFNα for recurrent craniopharyngiomas

PICO question	Literature search terms	No. of articles	No. included post-title review	No. included post-abstract review	Final no. included
P In children <19 years who have had a relapse or progression of a craniopharyngioma **I** does primary systemic IFNα **C** compared to resection/ radiotherapy/ conservative management **O** result in equivalent overall and progression-free survival, reduced cognitive impairment, reduced visual impairment, reduced hypothalamo-pituitary dysfunction?	1. exp Cranioparyngioma/ or craniopharyngioma*.mp. 2. limit 1 to "all child (0 to 18 years)" 3. relapse.mp. or Recurrence/ 4. recurrence.mp. 5. exp Disease Progression/ or progression.mp. 6. 3 or 4 or 5 7. 2 and 6 8. Interferon-alpha/ 9. interferon.mp. or exp Interferons/ 10. 8 or 9 11. 7 and 10	10	4	3	3

Author(s)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Plausible confounding	Dose-response gradient
Goldman et al., 2020(333)	Prospective cohort	Yes – no comparison to conventional treatment	No	No	Yes – small cohort of only 18 patients	No	No	No	No
Yeung et al., 2012(237)	Case series	Yes – no comparison to conventional treatment	No	No	Yes – case series of only 5 patients	Yes – single centre case series	No	No	No
Jakacki et al., 2000(236)	Prospective cohort	Yes – no comparison to conventional treatment	No	No	Yes – small cohort of only 15 patients	Yes – single centre	No	No	No

Author(s)	Summary of findings					Quality
	No. of events in IFNα group	No. of patients	No. of events in non-IFNα group	No. of patients	Pooled effect	
Goldman et al., 2020	Partial response 2 (1 sustained >3 months) Progression 8	18	N/A (no comparison to conventional treatments)	N/A	N/A	Very low
Yeung et al., 2012	Progression 1	5	N/A (no comparison to conventional treatments)	N/A	N/A	Very low
Jakacki et al., 2000	Progression 4 Side effects 9	14	N/A (no comparison to conventional treatments)	N/A	N/A	Very low

Appendix D: The Delphi consensus process

At least 50 and up to 80, potential Delphi consensus process participants were nominated by GDG members from across the UK, and also from Europe and the USA, and were chosen both for their recognised expertise in the management of paediatric craniopharyngiomas and to be representative of the multidisciplinary expertise required. One or two individual international peer experts, super specialists in the field, were also identified.

Recommendations that the GDG wished to make for which there was no evidence or in which the identified evidence was contradictory, were peer reviewed using two rounds of a Delphi consensus process, conducted through an electronic survey with the options of "support", "would support with modification", and "do not support". Responses allowed experts to state where a recommendation fell outside their subspeciality area of expertise: it was expected experts could not respond to every statement and that respondent numbers might be considerably reduced, and that there would be disagreement in very contentious areas. Experts were alerted to the forthcoming survey before the summer of 2016 and their email addresses provided by the GDG, verified individually by the project board (PB). The 1st round of the survey was run in September 2016 for at least 3 weeks, with two reminders. A recommendation was deemed to have reached consensus if 70% or more of the Delphi group participants who felt they had the expertise to comment on the recommendation, agreed with the statement or with a minor modification of it. All Delphi participants were offered the opportunity to comment on recommendations. Comments on recommendations that did not achieve consensus were reviewed by both the PB and the GDG; those recommendations in which modifications were likely to achieve consensus were modified and reviewed in a second Delphi consensus round. This was run in November 2016 for at least 2 weeks. The Delphi process for the guideline on the management of paediatric craniopharyngiomas is summarised in the tables below.

Recommendation	No. of participants	No. voting on recommend-ation	No. supporting WITHOUT modification	No. supporting WITH modification	% agreement	Summary of comments	Included in guideline
Round 1							
1. All CYP with suspected or confirmed craniopharyngioma should be managed in a tertiary paediatric endocrine centre by a lead paediatric endocrinologist with experience in pituitary tumours, nominated by and in liaison with the designated tertiary paediatric neuro-oncology team.	19	19	13	5	95%	Comments on the inclusion of specific reference to neurosurgery input, which is already implied in the rest of the guideline	Yes (3.1.1)
2. On completion of growth and puberty, CYP with craniopharyngiomas should be transferred to adult pituitary services.	19	18	10	8	100%	Comment on individualisation of timing	Yes with modifiers (3.1.6)
3. Any pituitary surgery on CYP should be attempted only in an age-appropriate tertiary setting with on-site peri-operative endocrine support.	19	19	17	1	95%	Comment on other support services (e.g. anaesthetics, neurorehabilitation, which is already implied in the rest of the guideline	Yes (3.1.3)
4. In CYP with suspected or confirmed craniopharyngiomas, surgery should be undertaken by the pituitary or paediatric neurosurgeon nominated by the respective adult pituitary or paediatric neuro-oncology MDT, who can offer all possible approaches (including transsphenoidal, transcranial, and endoscopic-assisted surgery).	19	18	10	5	83%	Comment on this only being possible for non-emergency procedures.	Yes (3.1.4)

Recommendation	No. of participants	No. voting on recommend-ation	No. supporting WITHOUT modification	No. supporting WITH modification	% agreement	Summary of comments	Included in guideline
5. A centralised national pituitary-specific advisory panel for review of images, histology and decision-making should be facilitated for discussion of complex cases.	19	18	11	4	83%	Comment on decision-making at the level of the local, not national MDT	Yes (3.1.5)
6. Given the rarity of pituitary tumours in children and young persons, a national registry should be developed for this patient group.	19	19	17	2	100%	None major	Yes (3.1.7)
7. The registry should provide the means by which the outcomes of patients managed with these guidelines can be monitored.	19	19	17	2	100%	Comment on the aim of a registry to track incidence, recurrence and treatment but not to audit outcomes	Yes (discarded as overlapping with 3.1.6)
8. Advanced multimodal imaging techniques (e.g. diffusion tensor imaging (DTI), perfusion-weighted imaging (PWI), magnetic resonance spectroscopy (MRS)) may be a useful adjunct to structural imaging in the preoperative assessment of paediatric craniopharyngiomas.	19	15	6	3	60%	Comments to reframe statement as a recommendation	Revised in Round 2
9. Baseline pituitary function testing at diagnosis including IGF-1, TSH, free T_4, LH, FSH, testosterone/ oestradiol, prolactin, 8 am cortisol, paired early morning plasma/ urine osmolalities, AFP and β-hCG concentrations should be measured prior to any intervention.	19	14	10	4	100%	Comment on this not always being possible in emergency setting, importance of prolactin and tumour markers as priority	Yes (3.2.1.3.a)

Recommendation	No. of participants	No. voting on recommend-ation	No. supporting WITHOUT modification	No. supporting WITH modification	% agreement	Summary of comments	Included in guideline
10. If possible, combined dynamic pituitary function tests of growth hormone and cortisol (with or without gonadotrophin, if age-appropriate) reserve should be considered at presentation before treatment to assess hypothalamo-pituitary function and inform the decision-making process.	19	12	8	2	83%	None major	Yes (3.2.1.3.c)
11. Definitive treatment of craniopharyngiomas by surgical resection or radiotherapy should not proceed without the availability of routine histopathology to confirm the diagnosis.	19	17	9	5	82%	Comments to reframe with statement on cyst fluid (12), and that biopsy can be performed as part of surgical resection in a single procedure	No – merged with (12) and revised in Round 2
12. Cyst fluid where available should be examined (cytology, crystals for birefringence) for features compatible with the diagnosis of a craniopharyngioma	19	14	5	1	43%	Comments to merge with (11) as one statement, and that cyst fluid is not additionally beneficial in the presence of solid tissue histology	No – merged with (11) and revised in Round 2
13. In patients with hydrocephalus secondary to craniopharyngioma cyst(s), primary cyst drainage is preferable to insertion of a ventriculoperitoneal shunt or external ventricular drain.	19	12	7	1	67%	None major	Yes (3.2.2.1.e)

Recommendation	No. of participants	No. voting on recommend-ation	No. supporting WITHOUT modification	No. supporting WITH modification	% agreement	Summary of comments	Included in guideline
14. Pre- and post-surgery dexamethasone (independent to any requirements for replacement hydrocortisone) for neuroprotection should be given for 48-72 hours to all paediatric craniopharyngioma patients undergoing craniotomy.	19	9	5	3	89%	Comments regarding the ambiguity of both statements and suggestion that statements be merged	No – merged with (15) and revised in Round 2
15. Pre- and post-surgery dexamethasone (independent to any requirements for replacement hydrocortisone) is not required for craniopharyngioma patients undergoing transsphenoidal resection.	19	9	5	1	67%		No – merged with (14) and revised in Round 2
16. Close observation for tumour progression rather than immediate radiotherapy is appropriate in selected cases of patients with residual solid tumour following surgical resection.	19	14	11	2	93%	None major	Yes (3.2.2.3.c)
17. The recommended gross tumour volume (GTV) is defined as the post-operative solid and cystic tumour complex.	19	7	6	0	86%	None	Yes (3.2.2.3.d)
18. The clinical target volume (CTV) margin is 5 mm modified to barriers of natural spread.	19	3	2	1	100%	None major	Yes (3.2.2.3.e)
19. The optimum dose fractionation regimen for the treatment of craniopharyngiomas is 54 Gy in 30 fractions treating 1 fraction daily for 6 weeks .	19	4	4	0	100%	None	Yes (3.2.2.3.f)

Recommendation	No. of participants	No. voting on recommend-ation	No. supporting WITHOUT modification	No. supporting WITH modification	% agreement	Summary of comments	Included in guideline
20. The optimum dose fractionation regimen for the treatment of craniopharyngiomas is 50 Gy in 30 fractions treating 1 fraction daily for 6 weeks.	19	3	0	0	0%	None	No – removed in favour of (19)
21. Post-treatment (surgery with or without radiotherapy) imaging interval in patients with a craniopharyngioma should be guided by individual patient factors and by the MDT.	19	16	14	1	94%	Comment on proposed scanning interval 3-4 monthly for 18 months then 6 monthly for 2 years	Yes (3.2.2.5.b)
22. All craniopharyngioma patients need a baseline visual assessment (to include visual acuity and visual fields where the patient is old enough) within three months of initial tumour treatment.	19	16	14	1	94%	None major	Yes (3.2.2.5.c)
23. Ongoing visual follow-up should be determined on an individual patient basis.	19	16	13	0	81%	Comment on proposed close visual monitoring for first 3-5 years of follow-up	Yes (3.2.2.5.d)
24. A combined pituitary function test (ITT/ LHRH with baseline thyroid function tests) is required within 6 weeks of initial tumour treatment to assess hypothalamo-pituitary function, particularly GH, ACTH and TSH deficiencies.	19	9	6	3	100%	None major – addition of word "dynamic" suggested and agreed	Yes (3.2.2.5.e)
25. An insulin tolerance test is recommended to diagnosed ACTH deficiency.	19	3	0	1	33%	Poor return on this statement with only 4 respondents with poor support. Comments on alternative testing, e.g. synacthen test	No

Recommendation	No. of participants	No. voting on recommend-ation	No. supporting WITHOUT modification	No. supporting WITH modification	% agreement	Summary of comments	Included in guideline
26. Ongoing endocrinology follow-up should be lifelong, with the frequency determined on an individual patient basis.	19	15	14	1	100%	Comment that this may not apply to all patients	Yes (3.2.2.5.f)
27. All craniopharyngioma patients require a baseline neuropsychological assessment around the time of diagnosis.	19	13	6	6	92%	Comments on pragmatism about timing of assessment which may be impeded by patient's consciousness or physical status, as well as availability of resources	Yes (3.2.1.4.a)
28. Patients with identified neuropsychological deficits require ongoing neuropsychological follow-up.	19	15	15	0	100%	None major	Yes (3.2.2.5.k)*
29. All craniopharyngioma patients who have been treated with radiotherapy require ongoing neuropsychological follow-up	19	13	12	1	100%	None major	Yes (3.2.2.5.k)*
30. A patient who develops a recurrent craniopharyngioma (cystic or solid) following initial complete resection and who has not previously been irradiated should be considered for further surgery in conjunction with radiotherapy.	19	15	12	3	100%	Comments on need for individualisation of treatment for recurrence	Yes (3.2.2.6.a)
31. A patient who develops a progressive primarily cystic craniopharyngioma following initial incomplete resection should have further cyst drainage prior to consideration of radiotherapy.	19	15	9	6	100%	Comment on need for individualisation of treatment for recurrence	Yes (3.2.2.6.b)

Recommendation	No. of participants	No. voting on recommend-ation	No. supporting WITHOUT modification	No. supporting WITH modification	% agreement	Summary of comments	Included in guideline
32. A patient who develops a progressive primarily solid craniopharyngioma following initial incomplete resection should be referred for radiotherapy.	19	13	8	5	100%	Comment on need for individualisation of treatment for recurrence, particularly of repeat resection prior to radiotherapy	Yes (3.2.2.6.c)
33. In patients who experience craniopharyngioma progression or recurrence following radiotherapy, a second course of radiotherapy should only be considered after all other therapeutic modalities have been explored.	19	13	12	1	100%	None major	Yes (3.2.2.6.d)
Round 2							
1. The role of advanced multimodal imaging techniques (e.g. diffusion tensor imaging (DTI), perfusion-weighted imaging (PWI), magnetic resonance spectroscopy (MRS)) as an adjunct to routine structural imaging in the pre-operative assessment of paediatric craniopharyngiomas has not been proven and requires further study before its routine use can be recommended.	28	23	21	2	100%	Comments that in most cases adding these techniques as part of standard MRI sequences are minimal time-wise, but further research needed	Yes (3.2.1.1.b)

Recommendation	No. of participants	No. voting on recommend-ation	No. supporting WITHOUT modification	No. supporting WITH modification	% agreement	Summary of comments	Included in guideline
2. Definitive treatment of craniopharyngioma by surgical resection of radiotherapy should not proceed without the availability of confirmatory pre- or peri-operative tissue histopathology or the examination of the characteristic cyst fluid for cytology and crystals for birefringence.	28	23	7	14	91%	Comments regarding exceptional situations where (a) emergency surgery is needed e.g. hydrocephalus, (b) a clear radiological diagnosis is possible, or (c) that surgery is felt to be too high-risk where a tissue diagnosis is not possible/ necessary.	Yes with modifiers (3.2.1.5.a)
3. Perioperative dexamethasone for a minimum of 48-72 hours with rapid tapering post-resection is required for neuroprotection in all paediatric craniopharyngioma patients undergoing craniotomy but not for transsphenoidal surgery unless there is cerebral oedema or wide opening of the cerebrospinal fluid space.	28	15	15	0	100%	None major	Yes (3.2.2.2.a)
4. The possibility of ACTH deficiency requires differentiating from dexamethasone-induced ACTH suppression, and may require assessment by insulin tolerance testing, serial morning cortisol/ ACTH or low dose synacthen stimulation on more than once occasion over time, to accurately define this.	28	14	12	2	100%	None major	Yes (3.2.2.5.h)

* Statements merged as part of same recommendation.

Appendix E: Gaps in the evidence & research recommendations

Having reviewed the evidence and sought consensus opinion on areas where evidence is contradictory or poor the GDG proposes that the following research questions be prioritised:

- What is the role of advanced multimodal imaging techniques and intraoperative MRI in the diagnosis and treatment of craniopharyngiomas in CYP?
- What is the diagnostic and prognostic role of immunohistochemical and genetic markers in CYP and their role in tailoring treatment (including the banking of tissue samples for research)?
- What are the short- and long-term outcomes of different neurosurgical approaches in the management of craniopharyngiomas?
- What is the efficacy and long-term safety profile of proton beam therapy in the treatment of craniopharyngiomas in CYP in comparison to photon beam therapy?
- What is the efficacy and long-term safety profile of stereotactic radiosurgery compared with conventional radiotherapy in CYP?
- What is the role, efficacy and long-term safety profile of intracystic therapies for managing cystic craniopharyngiomas?
- What is the optimum dose of hydrocortisone to be used in the peri-operative period in craniopharyngioma patients not receiving dexamethasone for peri-tumoral oedema?
- What is the pathophysiology of hypothalamic obesity and its associated disorders of sleep, behaviour, thermoregulation and appetite?
- What are the optimum treatment strategies for the management of hypothalamic obesity?
- What are the relative efficacies of the various treatments for sleep disorders in paediatric craniopharyngioma survivors?

The GDG also recognises that the full results of two prospective multicentre studies on paediatric craniopharyngioma, KRANIOPHARYNGEOM 2000 and KRANIOPHARYNGEOM 2007, have yet to be published. KRANIOPHARYNGEOM 2000 was a multicentre, multinational prospective observational study analysing the effects of various on non-randomised treatment variables which last reported outcomes in 2014(365), with even longer-term outcomes awaited. KRANIOPHARYNGEOM 2007 is the first multicentre randomised trial attempting to determine the optimum timing of radiotherapy in children >5 years with craniopharyngioma who have undergone a subtotal resection, the results of which are also pending. Data from both of these studies promise to provide high quality data on the optimum management of paediatric craniopharyngioma and will be included, if available, in the next review of this guideline.

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Children's Cancer and Leukaemia Group (CCLG) is a leading national charity and expert voice for all childhood cancers.

Each week in the UK and Ireland, more than 30 children are diagnosed with cancer. Our network of dedicated professional members work together in treatment, care and research to help shape a future where all children with cancer survive and live happy, healthy and independent lives.

We fund and support innovative world-class research and collaborate, both nationally and internationally, to drive forward improvements in childhood cancer. Our award-winning information resources help lessen the anxiety, stress and loneliness commonly felt by families, giving support throughout the cancer journey.

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