Craniopharyngioma in children: trends from a third consecutive single-centre cohort study

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Informed consent was not sought, as this was a retrospective study.

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HJM, FTR and ZH were involved in the acquisition of data, analysis of data, and drafting the manuscript. SB, HS, RH, OJ, DT, JG, NLD and KA were involved in the study conception and critical revision of the manuscript.

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Abstract

Object: The management of children with craniopharyngioma has evolved over time with a trend towards less invasive neurosurgical approaches as surgeons have sought to balance oncological control and treatment-related morbidity. To this end, the aim of this study was to evaluate the safety and effectiveness of our current management of children with craniopharyngioma when compared to previous cohorts managed at our centre.

Methods: A prospectively maintained database was searched over a 14-year period between 1st January 2005 and the 31st December 2018 to identify all children aged 17 years or less with a new diagnosis of craniopharyngioma. A retrospective case note review was performed for each child to extract data on their presentation, investigation, treatment, and outcome. Morbidity was assessed in the same fashion as in previous cohorts using the following categories: visual loss, pituitary dysfunction, hypothalamic dysfunction, neurological deficits, and cognitive impairment.

Results: In all, 59 children were identified with craniopharyngioma during the study period. A total of 92 operations were performed including cyst drainage (35/92; 38.0%), craniotomy and resection (30/92; 32.6%), and transsphenoidal resection (16/92; 17.4%). Approximately two thirds of all operations were performed using image guidance (66/92; 71.7%) and one third using endoscopy (27/92; 29.3%). The majority of children had adjuvant therapy comprising proton beam therapy (18/59; 30.5%) or conventional radiotherapy (16/59; 27.1%). The median follow up was 44 months (range 1 – 142 months) and approximately half the children had no evidence of residual disease on MRI (28/59; 47.5%). Of the remaining 31 children, there was a reduction in the volume of residual disease in 8 (8/59; 13.6%), stable residual disease in 18 (18/59; 30.5%), and growth in 5 (5/59; 8.5%). There was significantly reduced morbidity in all categories compared to our last cohort ($p < 0.05$).

Conclusions: Our institutional experience of paediatric craniopharyngioma confirms a trend toward less invasive neurosurgical procedures, most of which are now performed with the benefit of image guidance or endoscopy. Moreover, we have identified an expanding role for more targeted radiotherapy for children with residual disease. These advances have allowed for

78 comparable tumour control to our previous cohorts, but with significantly reduced morbidity and
79 mortality.

80 Key words: Surgery; Craniopharyngioma; Endoscopy; Image guidance; Outcomes

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Introduction

Craniopharyngioma is a rare but important intracranial tumour that continues to represent a considerable challenge to the paediatric neurosurgeon. It is defined by the World Health Organisation (WHO) histologically as a benign tumour (WHO grade I) but has often been described as behaving in a malignant manner because of its propensity to be located close to highly eloquent brain structures, and its propensity for local recurrence.[18] Both the tumour itself, and attempts to treat it, can result in considerable visual, endocrine, and cognitive morbidity.

Attitudes to the management of children with craniopharyngioma have evolved over time, in part reflecting a general trend towards less invasive neurosurgical approaches.[31] A survey of American paediatric neurosurgeons approximately 20 years ago revealed that the overwhelming majority favoured radical surgical resection.[32] At our own institution, our default management had been to perform radical resection where possible and to reserve radiotherapy for those children whose tumours had been incompletely resected or whose tumours had recurred. In a cohort of 75 children were treated between 1973 and 1994 the 10-year survival was 88%. Significant treatment-related morbidity was highlighted in this cohort, particularly hypothalamic dysfunction, and a 12% (9/75) mortality rate.[5]

In the following decade, we altered our management of children with craniopharyngioma to become more flexible, with an emphasis on reducing morbidity and mortality. In brief, children were stratified at presentation into those in whom it was deemed appropriate to attempt a radical resection, and those considered at high risk from radical resection in whom a subtotal resection or simple cyst aspiration was performed as part of a staged approach followed by radiotherapy either immediately or anticipated but deferred by virtue of the child's young age. In the subsequent cohort of 48 children treated between 1996 and 2004, the rate of tumour control was comparable, but the morbidity was significantly lower, and there was a 4% (2/48) morality rate.[36]

In the years since, we have continued to refine our management of children with craniopharyngioma, and in particular have made use of several technological advances such as image guidance and endoscopy to facilitate less invasive neurosurgical approaches, and proton

beam therapy to deliver more targeted radiotherapy. To this end, the aim of this study was to evaluate the safety and effectiveness of our current management of children with craniopharyngioma when compared to previous cohorts.

Methods

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement was used in the preparation of this section of the manuscript.[40]

The study was registered as a Service Evaluation study with the Great Ormond Street Hospital for Children NHS Foundation Trust Clinical Audit Committee and the University College London Hospitals NHS Foundation Trust Clinical Audit Committee. Informed consent was not sought, as this was a retrospective study.

Setting and Participants:

The study was conducted at Great Ormond Street Hospital for Children, which acts as the regional referral centre in North London for children with brain tumours, and the National Hospital for Neurology and Neurosurgery, where most of our patients are transitioned for continuing care once they enter adulthood.

Our current management of children with craniopharyngioma is modified according to their clinical presentation and imaging features but generally includes a combination of surgical resection and radiotherapy (Figure 1).

Before surgery, each case is discussed in a dedicated multidisciplinary meeting and managed jointly by the surgical and medical team, which includes endocrinologists, ophthalmologists, and radiation oncologists. A decision is then made on the surgical approach. Large cystic components are drained primarily. The decision to proceed with radical surgical resection is dependent on clinical and radiological features. Children who demonstrate hypothalamic dysfunction at presentation are more likely to have involvement of the hypothalamus on imaging; we are reluctant to attempt complete resection in these cases. De Vile *et al* described the association of pre-operative hypothalamic involvement on MRI with obesity.[4] Absence of the pituitary stalk,

displacement of the optic chiasm, and peri-tumoural hypothalamic oedema are all known to be associated with pre-operative hyperphagia and obesity.[24] Acute hydrocephalus is also a predictor of hypothalamic involvement.[6,25] The relationship of the tumour to the walls of the third ventricle, best seen in the coronal plane, defines hypothalamic involvement; increased signal change on T2-weighted and FLAIR sequence MRI, as well as contrast enhancement, predicts increased hypothalamic risk.[38] Increased risk is also associated with tumours that extended posterior to the mamillary bodies.[27] Tumours extending into the ventricular system are also known to be associated with increased risk and those with a retro-chiasmatic growth pattern and an incompetent diaphragm are associated with a higher post-operative BMI.[24,34]

In addition to clinical and anatomical factors, our decision to proceed with radical resection is also influenced by scoring systems that were published during this cohort (8,9).[26,28] These systems attempted to objectively define the degree of hypothalamic involvement and the associated risk of complete resection. On the basis of their 66 paediatric craniopharyngiomas, Puget *et al* published a simple three-point scoring system, based on coronal and sagittal MRI, where hypothalamic involvement was classified as 0 (no involvement), grade 1 (tumour abutting or displacing the hypothalamus), and grade 2 (hypothalamus significantly involved and no longer identifiable).[28] In another classification, the location of the tumour was defined as involving one of four areas: limited superiorly by the diaphragma sellae, below the optic chiasm and mamillary bodies, or above the latter two structures.[26] This last group is further subdivided into areas anterior and posterior to the mamillary bodies. Involvement of higher and more posterior structures was associated with higher risk.

During surgery, we frequently make use of image guidance and endoscopy depending on their availability and individual surgeon preference, in an attempt to reduce the risk of injury to the hypothalamus.

Following surgery, each case is rediscussed in the multidisciplinary meeting to consider the pathology findings, clinical progress, and post-operative imaging features. A decision is then made on ongoing management with proton beam radiotherapy, conventional radiotherapy, or simple surveillance with serial imaging.

All cases are recorded on a prospectively maintained database, and this database was searched over a 14-year period between 1st January 2005 and the 31st December 2018 to identify all children aged 17 years or less with a new diagnosis of craniopharyngioma.

Variables and data sources:

A retrospective case note review was performed for each child to extract data on their presentation, investigation, treatment, and outcome.

Data on each child's presentation included their age, gender, symptoms, and signs. Data on their investigation included the location and signal characteristics of the craniopharyngioma on Magnetic Resonance Imaging (MRI), and the presence of associated ventriculomegaly. Data on their treatment included both operative and non-operative interventions, and any associated complications. Data on their outcome included evidence of tumour control on post-operative imaging, morbidity, and mortality. Morbidity was assessed in the same fashion as in previous cohorts using the following categories: visual loss, pituitary dysfunction, hypothalamic dysfunction, neurological deficits, and cognitive impairment, as measured at last follow up (Table 1).[36] Cognitive impairment was evaluated according to educational requirements, which has the advantage of being easily identified in retrospective analyses. In each category, severity was rated between 0 (best) and 3 (worst).

Study size and statistical methods:

No formal power calculation was performed. Instead, the sample size was determined on a constraint-based pragmatic approach and on our previous cohort studies.[5,36] We considered a minimum of 50 children sufficient for meaningful comparison to previous cohorts, and it was estimated that this would be achieved over a 14-year period.

Data were analysed using with SPSS v 20.0 (IBM, Illinois, USA). The mean and standard deviation were calculated for parametric variables, and the median and interquartile ranges calculated for non-parametric variables. The Chi-square test and Fishers exact test were used to compare categorical variables. A value of $p < 0.05$ was considered statistically significant.

Results

Presentation and Investigation:

In all, 59 children were identified with craniopharyngioma during the study period. The median age was 8.5 years (range 1 – 17 years), and the male:female ratio 1.36:1. The most common presenting symptoms were headache (33/59; 55.9%), vomiting (25/59; 42.4%), and visual loss (22/59; 37.2%). Other common symptoms were related to endocrine dysfunction and included short stature (14/59; 23.7%), lethargy (11/59; 18.6%), and polydipsia and/or polyuria (8/58; 13.6%). Cognitive and behavioural symptoms were rare at presentation (4/59; 6.8%), and in two cases the craniopharyngioma was diagnosed incidentally following a minor head injury (2/59; 3.4%).

The most common signs were ophthalmic and included reduced visual acuity in one or both eyes (37/59; 62.7%), papilloedema and optic atrophy (13/59; 22.0%), restricted visual fields (8/59; 13.6%), and ophthalmoplegia (6/59; 10.2%). Other signs included ataxia (8/59; 13.6%) and a reduced level of consciousness (2/59; 3.4%).

The most common location for craniopharyngioma was suprasellar (38/59; 64.4%); in four of these cases the tumour extended into the third ventricle, in two cases into the posterior fossa, and in one case into the anterior fossa. In the remaining cases the craniopharyngioma was located in both the sellar and suprasellar region (14/59; 23.7%) or within the sellar region alone (7/59; 11.9%). In approximately a fifth of cases the craniopharyngioma appeared cystic (12/59; 20.3%) and a similar proportion appeared calcified (9/59; 15.3%). There was associated ventriculomegaly in 24 cases (24/59; 40.7%).

Treatment:

A total of 92 operations were performed in the 59 children. Overall, these operations were less invasive than in previous cohorts (Figure 2). The most common operation was cyst drainage (35/92; 38.0%), and in most of these cases a reservoir was left to allow access post-operatively (30/92; 32.6%). The other common operations were craniotomy and resection (30/92; 32.6%) and transsphenoidal resection (16/92; 17.4%). Five children underwent insertion of a

ventriculoperitoneal shunt (5/92; 5.4%). Approximately two thirds of all operations were performed using image guidance (66/92; 71.7%) and one third using endoscopy, including transsphenoidal and transventricular approaches (27/92; 29.3%).

Post-operative complications included CSF leak (4/92; 4.3%) and wound infection (3/92; 3.3%). One child had a post-operative intracerebral haematoma that required surgical evacuation, one child developed hydrocephalus that required a ventriculoperitoneal shunt, and one child had seizures that were managed medically. The median length of stay was 10 days (range 1 – 44 days).

The majority of children had adjuvant therapy including proton beam therapy (18/59; 30.5%) or conventional radiotherapy, typically 50 Gy in 30 fractions (16/59; 27.1%). Three children had interferon-alpha therapy for cystic recurrence.

Post-therapy complications included one child who developed vasculopathy following proton beam therapy.

Outcome:

The median follow up was 44 months (range 1 – 142 months). The actuarial progression free survival curve is illustrated in Figure 3, and the overall 10 year progression free survival was estimated to be 68.8%. At last follow up, approximately half the children had no evidence of residual disease on MRI (28/59; 47.5%). Of the remaining 31 children, there was a reduction in the volume of residual disease in 8 (8/59; 13.6%), stable residual disease in 18 (18/59; 30.5%), and growth in 5 (5/59; 8.5%).

One child with growth of residual disease died, and this was thought to be due to tumour progression (1/59; 1.7%). The other four children with growth of residual disease remain under active management.

The visual loss, pituitary dysfunction, hypothalamic dysfunction, neurological deficits, and cognitive impairment before and after treatment are summarised in Table 2 and Figure 4. After treatment, children were significantly less likely to have visual loss, but more likely to have pituitary dysfunction, compared to before treatment ($p < 0.01$ in both cases).

There was an obvious trend towards reduced morbidity in all categories compared to our previous cohorts. Before treatment, the visual loss, pituitary dysfunction, hypothalamic dysfunction, neurological deficits, and cognitive impairment, were similar to the last cohort ($p > 0.1$ in all cases). After treatment, however, the visual loss, pituitary dysfunction, hypothalamic dysfunction, neurological deficits, and cognitive impairment, were all significantly reduced compared to the last cohort ($p < 0.05$ in all cases)

Discussion

Principal findings:

In our most current cohort of children with craniopharyngioma, we have confirmed a clear and growing trend towards the use of less invasive neurosurgical procedures, most of which are now performed with the benefit of image guidance or endoscopy. Moreover, there is an expanding role for more targeted radiotherapy for children with residual disease. These advances have allowed for comparable tumour control to our previous cohorts, but with significantly reduced morbidity and mortality.

Comparison with other studies:

Our finding of a trend towards less invasive neurosurgical procedures, and increased use of image guidance or endoscopy, is in keeping with the literature. In a recent analysis of patents and peer-reviewed publications within neurosurgery, we found that image guidance and endoscopy were among the top five performing technology clusters over the last 50 years.[22] We speculate that the increased availability and familiarity of image guidance and endoscopy in this cohort compared to previous cohorts allowed for more frequent cyst drainage and transsphenoidal resection respectively.

The use of image guidance in neurosurgery has promulgated since the development of frameless techniques in the 1980's and 1990's.[19,30] Image guidance has two distinct roles in neurosurgery: first, to better define the surgical approach; and second, to allow for unambiguous tissue dissection, particularly in the context of tumour resection. Currently, image guidance platforms are largely used for the former, and several groups have reported their use to facilitate less invasive

neurosurgical approaches when managing children with craniopharyngioma and other skull base tumours.[9,12,14,16,17,39] Although image guidance was used in approximately two thirds of all operations in our current cohort, it was used for almost all operations in the latter years, and we now consider it a standard of care. In the near future, intra-operative imaging with ultrasound, CT, or MRI, may routinely allow for an increased extent of tumour resection, while preserving highly eloquent brain structures, and this is already the case in many centres.[8,11,23]

The use of endoscopy in neurosurgery has also increased since the development of the SELFOC® lens (Go!Foton New Jersey, USA), Charge-Coupled Device (CCD), and fibre-optic light source, in the 1980's.[10] Endoscopy allows for an improved viewing angle, higher magnification, and increased illumination, when operating through a narrow surgical corridor, making it ideally suited to the management of deep-seated tumours such as craniopharyngioma. A number of groups have reported the use of the endoscopic intraventricular and endoscopic endonasal transsphenoidal approaches when managing children with craniopharyngioma.[2,7,12,14,16,17] Advances such as 3-Dimensional and High Definition endoscopy may further improve visualisation in the coming years.[21]

Alongside the aforementioned trend towards the use of less invasive neurosurgical procedures when managing children with craniopharyngioma, there has also been a trend towards the use of more targeted radiotherapy including proton beam therapy. There remains limited comparative evidence in the literature for the use of proton beam radiotherapy over external beam radiotherapy. Nonetheless, several retrospective studies have suggested that proton beam radiotherapy is at least as safe and effective as external beam therapy, and that worldwide a growing number of children are being treated at proton centres.[1,15,41]

The outcome of our new, less invasive, management paradigm has been a significant reduction in morbidity and mortality rates in our current cohort when compared to previous cohorts of children with craniopharyngioma, while maintaining good tumour control rates. These findings are consistent with the literature. In a recent systematic review, Clark *et al* identified 109 studies reporting the outcome of 531 children that underwent treatment for craniopharyngioma, and concluded that gross total resection was associated with increased risk of endocrine dysfunction and neurological deficits compared to subtotal resection and radiotherapy.[3]

Our treatment related morbidity and morbidity rates compare favourably to reports from other high volume centres. In a recent narrative review, Muller *et al* found that following treatment the rate of permanent diabetes insipidus was reported to be between 40 and 93% and the rate of growth hormone deficiency was between 70 and 92%, compared with a rate of 61% with pituitary dysfunction in our current cohort.[25] The rate of hypothalamic dysfunction such as obesity was also found to be high, reaching up to 55%, compared with 17% in our current cohort.[25] Similarly, the rate of neurological deficits such as hemiparesis was reported to be 8%, and cognitive impairment was 18%, compared with a rate of 7% and 17% respectively in our current cohort.[25]

Other centres that have adopted analogous management paradigms, and have taken great care to spare the hypothalamus, have reported similarly favourable outcomes. Puget *et al* reported no new cases of hyperphagia, morbid obesity, or behavioural dysfunction, in a cohort of 22 children.[28] Mallucci *et al* also reported no new of cases of hyperphagia or morbid obesity, in a cohort of 20 patients.[20]

At last follow up, 91.5% (54/59) of our current cohort of children with craniopharyngioma had no or stable residual disease on MRI, with the remaining five children showing tumour progression, and one tumour-related death. Other centres have also achieved good tumour control rates following subtotal resection when followed by contemporary radiotherapy. Stripp *et al* reported that 84% of children and young adults had tumour control at 10 years following subtotal resection and radiotherapy when compared to only 42% of following subtotal resection alone.[35] Karavitaki *et al* reported that 77% of patients had tumour control at 10 years following subtotal resection and radiotherapy compared to 38% following subtotal resection alone.[13] Schoenfeld *et al* reported that 73% of patients had tumour control at 2 years compared to 36% following subtotal resection alone.[33]

Limitations:

The present study has several limitations. Morbidity was assessed in the same fashion as in previous cohorts and, while less detailed than reported by other groups, has allowed for meaningful comparison to our previous cohorts. The median follow up of 44 months was short, in part due to the fact that many of our patients transition to other hospitals once they enter adulthood, but did

allow for evaluation of tumour control on post-operative imaging, morbidity, and mortality. The sample size of 59 children was small because craniopharyngioma is rare, but nonetheless met our *a priori* minimum of 50 children.

More generally, although the cases were recorded on a prospectively maintained database, the data was drawn from a retrospective case note review, and was therefore liable to inherent disadvantages such as incomplete or inaccurate data, selection bias, and lack of control.

Conclusions

Survival rates craniopharyngioma are good, with the majority of children expected to reach adulthood. However, despite its benign histology the treatment-related morbidity for craniopharyngioma, and the propensity for local tumour recurrence, have meant that hitherto many children have faced a lifetime of medical and neurosurgical intervention.

Our third consecutive cohort of children with craniopharyngioma confirms a trend toward less invasive neurosurgical procedures and more targeted radiotherapy. This trend is associated with a considerable reduction in morbidity and mortality following treatment, while maintaining good tumour control rates.

In the coming years, our focus will now be on maintaining acceptable morbidity and mortality, while increasing the effectiveness of treatment, particularly for children with tumours that involve critical structures such as the hypothalamus, or appear to have a particular biological propensity for recurrence. We speculate that innovative treatments such as targeted medical therapy[37] or high intensity focused ultrasound (HIFU)[29], may play a role in achieving this goal, alongside continued refinement of our management paradigm.

References

1. Bishop AJ, Greenfield B, Mahajan A, Paulino AC, Okcu MF, Allen PK, et al: Proton beam therapy versus conformal photon radiation therapy for childhood craniopharyngioma: multi-institutional analysis of outcomes, cyst dynamics, and toxicity. **Int J Radiat Oncol Biol Phys 90:**354-361, 2014
2. Cappabianca P, Cavallo LM, Esposito F, De Divitiis O, Messina A, De Divitiis E: Extended endoscopic endonasal approach to the midline skull base: the evolving role of transsphenoidal surgery. **Adv Tech Stand Neurosurg 33:**151-199, 2008
3. Clark AJ, Cage TA, Aranda D, Parsa AT, Auguste KI, Gupta N: Treatment-related morbidity and the management of pediatric craniopharyngioma: a systematic review. **J Neurosurg Pediatr 10:**293-301, 2012
4. de Vile CJ, Grant DB, Hayward RD, Kendall BE, Neville BG, Stanhope R: Obesity in childhood craniopharyngioma: relation to post-operative hypothalamic damage shown by magnetic resonance imaging. **J Clin Endocrinol Metab 81:**2734-2737, 1996
5. De Vile CJ, Grant DB, Kendall BE, Neville BG, Stanhope R, Watkins KE, et al: Management of childhood craniopharyngioma: can the morbidity of radical surgery be predicted? **J Neurosurg 85:**73-81, 1996
6. De Vile CJ, Grant DB, Hayward RD, Stanhope R: Growth and endocrine sequelae of craniopharyngioma. **Arch Dis Child 75:**108-114, 1996
7. Delitala A, Brunori A, Chiappetta F: Purely neuroendoscopic transventricular management of cystic craniopharyngiomas. **Childs Nerv Syst 20:**858-862, 2004
8. Giordano M, Samii A, Lawson McLean AC, Bertalanffy H, Fahlbusch R, Samii M, et al: Intraoperative magnetic resonance imaging in pediatric neurosurgery: safety and utility. **J Neurosurg Pediatr 19:**77-84, 2017
9. Hayhurst C, Williams D, Yousaf J, Richardson D, Pizer B, Mallucci C: Skull base surgery for tumors in children: long-term clinical and functional outcome. **J Neurosurg Pediatr 11:**496-503, 2013
10. Hellwig D, Tirakotai W, Riegel T, Heinze S, Bertalanffy H: Endoscopy in neurosurgery. **Dtsch Arztebl 104:**185-191, 2007

11. Hofmann BM, Nimsky C, Fahlbusch R: Benefit of 1.5-T intraoperative MR imaging in the surgical treatment of craniopharyngiomas. **Acta Neurochir (Wien) 153:**1377-1390; discussion 1390, 2011
12. Jane JA, Jr., Prevedello DM, Alden TD, Laws ER, Jr.: The transsphenoidal resection of pediatric craniopharyngiomas: a case series. **J Neurosurg Pediatr 5:**49-60, 2010
13. Karavitaki N, Cudlip S, Adams CB, Wass JA: Craniopharyngiomas. **Endocr Rev 27:**371-397, 2006
14. Kim K, Yeon JY, Seol HJ, Shin HJ: Transventricular endoscopic biopsy of suprasellar tumors: a pediatric case series. **Childs Nerv Syst 29:**1285-1291, 2013
15. Laffond C, Dellatolas G, Alapetite C, Puget S, Grill J, Habrand JL, et al: Quality-of-life, mood and executive functioning after childhood craniopharyngioma treated with surgery and proton beam therapy. **Brain Inj 26:**270-281, 2012
16. Leng LZ, Greenfield JP, Souweidane MM, Anand VK, Schwartz TH: Endoscopic, endonasal resection of craniopharyngiomas: analysis of outcome including extent of resection, cerebrospinal fluid leak, return to preoperative productivity, and body mass index. **Neurosurgery 70:**110-123; discussion 123-114, 2012
17. Locatelli D, Massimi L, Rigante M, Custodi V, Paludetti G, Castelnuovo P, et al: Endoscopic endonasal transsphenoidal surgery for sellar tumors in children. **Int J Pediatr Otorhinolaryngol 74:**1298-1302, 2010
18. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al: The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. **Acta Neuropathol 131:**803-820, 2016
19. Maciunas RJ, Galloway RL, Jr., Fitzpatrick JM, Mandava VR, Edwards CA, Allen GS: A universal system for interactive image-directed neurosurgery. **Stereotactic and functional neurosurgery 58:**108-113, 1992
20. Mallucci C, Pizer B, Blair J, Didi M, Doss A, Upadrasta S, et al: Management of craniopharyngioma: the Liverpool experience following the introduction of the CCLG guidelines. Introducing a new risk assessment grading system. **Childs Nerv Syst 28:**1181-1192, 2012
21. Marcus HJ, Hughes-Hallett A, Cundy TP, Di Marco A, Pratt P, Nandi D, et al: Comparative Effectiveness of 3-Dimensional vs 2-Dimensional and High-Definition vs Standard-

Definition Neuroendoscopy: A Preclinical Randomized Crossover Study. **Neurosurgery 74:**375-381, 2014

22. Marcus HJ, Hughes-Hallett A, Kwasnicki RM, Darzi A, Yang GZ, Nandi D: Technological innovation in neurosurgery: a quantitative study. **J Neurosurg:**1-8, 2015
23. Marcus HJ, Vercauteren T, Ourselin S, Dorward NL: Intraoperative Ultrasound in Patients Undergoing Transsphenoidal Surgery for Pituitary Adenoma: Systematic Review [corrected]. **World Neurosurg 106:**680-685, 2017
24. Mortini P, Gagliardi F, Bailo M, Spina A, Parlangeli A, Falini A, et al: Magnetic resonance imaging as predictor of functional outcome in craniopharyngiomas. **Endocrine 51:**148-162, 2016
25. Muller HL: Childhood craniopharyngioma: treatment strategies and outcomes. **Expert Rev Neurother 14:**187-197, 2014
26. Muller HL: Preoperative staging in childhood craniopharyngioma: standardization as a first step towards improved outcome. **Endocrine 51:**1-3, 2016
27. Muller HL, Gebhardt U, Teske C, Faldum A, Zwiener I, Warmuth-Metz M, et al: Post-operative hypothalamic lesions and obesity in childhood craniopharyngioma: results of the multinational prospective trial KRANIOPHARYNGEOM 2000 after 3-year follow-up. **Eur J Endocrinol 165:**17-24, 2011
28. Puget S, Garnett M, Wray A, Grill J, Habrand JL, Bodaert N, et al: Pediatric craniopharyngiomas: classification and treatment according to the degree of hypothalamic involvement. **J Neurosurg 106:**3-12, 2007
29. Quadri SA, Waqas M, Khan I, Khan MA, Suriya SS, Farooqui M, et al: High-intensity focused ultrasound: past, present, and future in neurosurgery. **Neurosurg Focus 44:**E16, 2018
30. Roberts DW, Strohbehn JW, Hatch JF, Murray W, Kettenberger H: A frameless stereotaxic integration of computerized tomographic imaging and the operating microscope. **J Neurosurg 65:**545-549, 1986
31. Sainte-Rose C, Puget S, Wray A, Zerah M, Grill J, Brauner R, et al: Craniopharyngioma: the pendulum of surgical management. **Childs Nerv Syst 21:**691-695, 2005
32. Sanford RA: Craniopharyngioma: results of survey of the American Society of Pediatric Neurosurgery. **Pediatr Neurosurg 21 Suppl 1:**39-43, 1994

33. Schoenfeld A, Pekmezci M, Barnes MJ, Tihan T, Gupta N, Lamborn KR, et al: The superiority of conservative resection and adjuvant radiation for craniopharyngiomas. **J Neurooncol 108:**133-139, 2012
34. Steno J, Bizik I, Steno A, Matejcik V: Craniopharyngiomas in children: how radical should the surgeon be? **Childs Nerv Syst 27:**41-54, 2011
35. Stripp DC, Maity A, Janss AJ, Belasco JB, Tochner ZA, Goldwein JW, et al: Surgery with or without radiation therapy in the management of craniopharyngiomas in children and young adults. **Int J Radiat Oncol Biol Phys 58:**714-720, 2004
36. Thompson D, Phipps K, Hayward R: Craniopharyngioma in childhood: our evidence-based approach to management. **Childs Nerv Syst 21:**660-668, 2005
37. Tritos NA: Is there a role for targeted medical therapies in patients with craniopharyngiomas? **Future Oncology 11:**3221-3223, 2015
38. Van Gompel JJ, Nippoldt TB, Higgins DM, Meyer FB: Magnetic resonance imaging-graded hypothalamic compression in surgically treated adult craniopharyngiomas determining postoperative obesity. **Neurosurg Focus 28:**E3, 2010
39. van Lindert EJ, Ingels K, Mylanus E, Grotenhuis JA: Variations of endonasal anatomy: relevance for the endoscopic endonasal transsphenoidal approach. **Acta Neurochir (Wien) 152:**1015-1020, 2010
40. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP: The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. **Lancet 370:**1453-1457, 2007
41. Winkfield KM, Linsenmeier C, Yock TI, Grant PE, Yeap BY, Butler WE, et al: Surveillance of craniopharyngioma cyst growth in children treated with proton radiotherapy. **Int J Radiat Oncol Biol Phys 73:**716-721, 2009

466 **Tables**

467 Table 1.

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469 Table 2.

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Figures

Figure 1. Illustrative case of an 8 year-old girl that presented with headache, vomiting, and blurred vision. (a) Pre-operative T1-weighted MRI Brain demonstrating sellar and suprasellar craniopharyngioma, (b) Post-operative T1-weighted MRI brain following extended transsphenoidal resection of the craniopharyngioma, and (c) Post-treatment T1-weighted MRI brain following Proton Beam Therapy.

Figure 2. Chart illustrating the varying number of cyst aspirations, transsphenoidal resections, and craniotomy and resections in (a) the 2005 to 2018 cohort, and (b) the 1996 to 2004 cohort.

Figure 3. Kaplan-Meier curve illustrating the actuarial progression free survival for the 2005 to 2018 cohort. Time was measured from the initial surgery. Recurrence was determined by post-operative imaging.

Figure 4. Graph illustrating morbidity before and after treatment, in the present and previous cohorts. In each category, the severity is reported as a proportion of the maximum possible score (0% = no patients have any morbidity; 100% = all patients have maximal morbidity).