Temporal trends in craniopharyngioma management and long-term endocrine outcomes: A multicentre cross-sectional study

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Abstract

Background: The optimal management of craniopharyngiomas remains controversial.

Objectives: To examine temporal trends in the management of craniopharyngioma with a focus on endocrine outcomes.

Methods: This was a cross-sectional, multicentre study. Patients treated between 1951 and 2015 were identified and divided into four quartiles. Demographics, presentation, treatment and outcomes were collected.

Results: In total, 142 patients with childhood-onset craniopharyngioma (48/142; 34%) and adult-onset disease (94/142; 66%) were included. The median follow-up was 15 years (IQR 5-23 years). Across quartiles, there was a significant trend towards using transsphenoidal surgery (P < .0001). The overall use of radiotherapy was not different among the four quartiles (P = .33). At the latest clinical review, the incidence of GH, ACTH, gonadotrophin deficiencies and anterior panhypopituitarism fell significantly across the duration of the study. Anterior panhypopituitarism was not

Ziad Hussein and Nigel Glynn should be considered joint first authors.
Maralyn Druce and Stephanie E. Baldeweg should be considered joint last authors.

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INTRODUCTION

Craniopharyngiomas are embryonic neoplasms of the sellar and parasellar region. With bimodal age distribution, craniopharyngiomas can manifest during childhood and adult life with pituitary and hypothalamic comorbidities from direct tumour infiltration and subsequent treatment. Pathologically, craniopharyngiomas are classified into two distinct variants; adamantinomatous subtype occurs mainly in paediatric patients and papillary subtype which is exclusive to adult population.

The location of the tumour in close approximation to vital intracranial structures and the risk of surgical damage to the hypothalamo-pituitary region have led to a growing trend towards more conservative surgery, aiming to preserve hypothalamic structures in particular, with a greater reliance on postoperative radiotherapy. It is not clear, however, whether this modern surgical approach is associated with improved long-term outcomes. Moreover, there is no consensus on the selection of patients for prophylactic radiotherapy or the optimal time to apply this treatment.

Recurrence is a common complication of craniopharyngiomas after initial therapy. Subsequent management of relapsed disease is often considered technically difficult with potentially increased morbidity and mortality.

In this multicentre clinical study, we investigated the management and outcomes of a large cohort of patients with craniopharyngioma from three tertiary endocrine centres in the United Kingdom. The primary aim of this study was to examine temporal trends in the management of craniopharyngioma and their impact on long-term patient’s endocrine function.

METHODS

In organizing this review of our clinical practice, we referred to the Health Research Authority online decision tool http://www.hra-decisiontools.org.uk/research/ which confirmed that Research approval was not required. This study was a multicentre cross-sectional study at three specialist pituitary services in London: Charing Cross Hospital, St Bartholomew’s Hospital and University College London Hospital. A search of electronic databases at each centre in 2015 identified all patients currently attending the clinic who were previously treated for craniopharyngioma. We performed a retrospective review of the case notes of all identified patients.

2.1 Data collection

Patients’ demographics, clinical presentation, treatment modalities and tumour regrowth were collected. In addition, details of patients’ outcomes including endocrine and metabolic outcomes were extracted. The cohort was divided into two groups, childhood-onset craniopharyngioma (COCP), defined as presentation before the age of 18 years, and adult-onset craniopharyngioma (AOCP), defined as presentation from 18 years of age onwards. Data related to tumour-directed treatment were collected about date and mode of surgery: transcranial (TCS) versus transsphenoidal surgery (TSS).

Prophylactic radiotherapy was defined as adjuvant radiotherapy administered after primary resection with the intention of preventing tumour regrowth, while therapeutic radiotherapy was defined as cranial irradiation administered for postoperative residual tumour postsurgery.

Tumour regrowth was defined as the need for further tumour-directed treatment (surgery or radiotherapy). Histopathological tumour subtype (adamantinomatous versus papillary) was recorded when available.

Persistent and late-developing complications including hypopituitarism, the presence of hyperlipidaemia and hyperglycaemia as well as anthropometric measurements were recorded as per the latest clinical review. The presence of hypertension, hyperlipidaemia and type two diabetes mellitus were defined when patients were prescribed antihypertensives, lipid-lowering agents and antidiabetic medications, respectively.
Pituitary hormone deficiencies were defined as follows: in the case of ACTH and TSH deficiency, patients were deficient if they were prescribed glucocorticoid and thyroxine replacement, respectively. Patients with diagnosis of primary hypothyroidism, recorded in the notes, were not included in the TSH deficient cohort. With respect to sex steroid deficiency, postmenopausal women with inappropriately normal or low serum gonadotrophins were gonadotrophin-deficient. Premenopausal women with amenorrhoea and nonelevated gonadotrophins were defined as three or more pituitary hormone deficiencies defined as three or more deficiencies were considered to be deficient in gonadotrophins. Men were gonadotrophin-deficient if they were prescribed testosterone replacement at last follow-up or if 9 AM serum testosterone concentration was low in the presence of inappropriately normal or low serum gonadotrophins. Patients with evidence of growth hormone (GH) deficiency on results of stimulation test or those currently treated with GH (peak serum GH < 3 µg/dL) were recorded as GH-deficient. In addition, patients with multiple pituitary hormone deficiencies defined as three or more deficiencies were considered to be deficient in GH. Anterior panhypopituitarism was considered when there was loss of three or more pituitary hormones. Patients were recorded as having cranial diabetes insipidus if they were prescribed maintenance desmopressin.

### Temporal trends

We divided the cohort into four consecutive groups. This was defined by the number of patients. Quartiles one and four contained 36 patients, while quartiles two and three contained 35 patients. Analysis of these equivalent size patient groups enabled meaningful evaluation of temporal trends in management, regrowth and complications. The first quartile contained the initial group of patients treated from the year 1951 onwards and the fourth quartile contained the most recently treated cases up to and including the year 2015. Dividing the cohort based on the date of surgery would result in unequal sized groups which are less amenable to statistical analysis.

### Statistical analysis

Basic data were evaluated using descriptive statistics. Median and interquartile range (IQR) were used to describe data not normally distributed. Chi-square test was used to compare categorical variables including the trend among investigator-defined treatment quartiles. Significance was defined as $P$-value < .05.

### Results

#### 3.1 Patients' characteristics and initial clinical presentation

Data from 142 patients with COCP (48/142; 34%) and AOCP (94/142; 66%) were analysed in this study. The cohort was divided into 4 quartiles (Table 1). In COCP, the median age at diagnosis was 9 years (IQR 6-14 years). In AOCP, the median age at diagnosis was 36 years (IQR 25-51 years). Within COCP group, 30 patients were boys (30/48; 63%) and 18 were girls (18/48; 37%) with no gender predilection ($P = .16$). Within AOCP group, 49 patients were men (49/94; 52%) and 45 were women (45/94; 48%) with no gender predilection ($P = .76$). There was no gender difference between the two groups ($P = .28$).

Data on initial clinical presentation were available for variable number of patients. Visual disturbance was the presenting symptom in 84 patients of both age of onset groups (84/111; 76%) (including 17 patients presented with combined visual and hormonal disturbance), 21 COCP (21/29; 72%) and 63 AOCP (63/82; 77%). Thirty-five patients (35/109; 32%) presented with pituitary dysfunction (including 17 patients presented with combined visual and hormonal disturbance), 14 COCP (14/27; 52%) and 21 AOCP (21/82; 26%). Pituitary dysfunction was more common in COCP than AOCP ($P = .01$). Details of individual pituitary hormone deficiency at presentation with both onset of disease groups are as follows: GH deficiency occurred in 8 patients (8/11; 73%), and 12 patients (12/44; 27%) had secondary hypogonadism. Nine patients (9/34; 26%) had ACTH deficiency, and 11 patients (11/43; 26%) presented with secondary hypothyroidism.

#### Table 1 The distribution of all craniopharyngioma patients, those who had transsphenoidal surgery in the full cohort and those with childhood-onset craniopharyngioma, those received radiotherapy, and those suffered tumour regrowth across the four quartiles

<table>
<thead>
<tr>
<th>Number</th>
<th>Qtr1</th>
<th>Qtr2</th>
<th>Qtr3</th>
<th>Qtr4</th>
</tr>
</thead>
<tbody>
<tr>
<td>COCP</td>
<td>17 (47%)</td>
<td>17 (49%)</td>
<td>14 (40%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>AOCP</td>
<td>19 (53%)</td>
<td>18 (51%)</td>
<td>21 (60%)</td>
<td>36 (100%)</td>
</tr>
<tr>
<td>TSS in the full cohort</td>
<td>7/25 (28%)</td>
<td>8/26 (31%)</td>
<td>16/35 (45%)</td>
<td>31/36 (86%)</td>
</tr>
<tr>
<td>TSS in COCP group</td>
<td>(1/11; 9%)</td>
<td>(3/13, 23%)</td>
<td>(4/12, 33%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>20/35 (57%)</td>
<td>26/35 (74%)</td>
<td>25/35 (71%)</td>
<td>15/33 (45%)</td>
</tr>
<tr>
<td>Tumour regrowth</td>
<td>8/36 (29%)</td>
<td>15/35 (43%)</td>
<td>15/35 (43%)</td>
<td>13/36 (36%)</td>
</tr>
</tbody>
</table>

Abbreviations: AOCP, adult-onset craniopharyngioma; COCP, childhood-onset craniopharyngioma; N/A, not applicable; Qtr, quartile; TSS, transsphenoidal surgery.
Eight patients (8/28; 29%) presented with anterior panhypopituitarism, and cranial diabetes insipidus occurred in 5 patients (5/47; 11%).

Headache was the presenting symptom in 11 patients of both age of onset groups (11/105; 9%), 6 COCP (6/23; 26%) and 5 AOCP (5/82; 6%). Headache was more common in the COCP group (P = .006).

3.2 | Treatment

Details of technique for primary surgical excision were available for 125 patients, 36 COCP (36/125; 29%) and 89 AOCP (89/125; 71%). TSS was performed on 62 patients (62/125; 50%), 8 COCP (8/36; 22%) and 54 AOCP (54/89; 61%)—TSS was used more frequently in the AOCP group (P < .0001). TCS was performed on 63 patients (63/125; 50%) in the study group, 28 COCP (28/36, 78%) and 35 AOCP (35/89; 39%)—TCS was significantly more common in the COCP group (P < .0001). Cyst aspiration was performed on 14 patients, nine with COCP (9/36; 25%) and five with AOCP (5/89; 6%). Details of operating surgeons were available for 90 patients, 22 patients (22/71; 31%) in quartiles one and two and 68 patients (68/71; 96%) in quartiles three and four. Fifty patients underwent operations at the three participating centres by experienced neurosurgeons (MP, JG, ND, NM, DP, IA, GA and LA). Fifty patients had their operation overseas.

There was a significant trend across the study period towards using TSS for craniopharyngioma resection from 28% in quartile one to 86% in quartile four (P < .0001) (Table 1; Figure 1). However, the trend of using TSS was not significantly maintained when the COCP group was analysed separately (P = .163; Table 1).

Histological data were available for 47 AOCP (47/50; 94%). Thirty-six (36/47; 76%) had adamantinomatous craniopharyngioma, while 11 (11/47; 23%) had papillary craniopharyngioma. Histology reports were available for only three COCP all of whom were of the adamantinomatous subtype.

Data for radiotherapy were available for 138 patients. In total, 86 patients (86/138; 62%) received postoperative radiotherapy, 33 patients (33/86; 38%) and 53 patients (53/86; 62%) with COCP and AOCP, respectively, with no association with age of onset (P = .2). Fifty patients had radiotherapy type and dose recorded. Forty-nine patients (49/50; 98%) received conventional conformal radiotherapy, 4 patients received 25-45 Gray and 39 patients received 50-55 Gray. Sixty Gray was administered in one patient and five patients had no radiotherapy dose recorded. One patient (1/49; 2%) had gamma knife radiosurgery.

Prophylactic radiotherapy was given in 56 patients (56/86; 65%), and therapeutic radiotherapy was administered in 30 patients (30/86; 35%). The temporal trend of using radiotherapy across all four quartiles during the time course of the study was not significantly different (P = .33) (Table 1; Figure 2). There was no significant difference in the use of radiotherapy between those underwent TSS (32/62; 52%) and those had TCS (40/63; 63%; P = .17).

3.3 | Tumour regrowth and outcome

The median follow-up was 15 years (IQR 5-23 years). In total, craniopharyngioma regrowth occurred in more than one-third of the patients (51/142; 36%) with median time of 3 years (IQR 1-6 years). There was no significant difference in tumour regrowth between COCP (16/48; 33%) and AOCP (35/94; 37%) (P = .4).

Among those treated with primary surgery and prophylactic radiotherapy (n = 56), 13 patients had regrowth (13/56; 23%); 12 patients needed further surgery and one patient was treated expectantly. Among those treated with surgery and no prophylactic radiotherapy (n = 86), 38 patients suffered craniopharyngioma regrowth (38/86; 44%), of which 24 patients (24/38; 63%) had further surgery and therapeutic radiotherapy, 7 patients (7/38; 18%) needed surgery, 6 patients (6/38; 16%) had therapeutic radiotherapy only, and one patient (1/38; 3%) was treated expectantly. Tumour regrowth was higher in patients treated with surgery only than those who
surgery and prophylactic radiotherapy ($P = .01$). Tumour regrowth was not associated with the histological type of craniopharyngioma in both age of onset groups ($P = 1.0$). There was no significant trend in craniopharyngioma regrowth across the four quartiles during the time course of the study ($P = .15$) (Table 1; Figure 3).

3.4 | Endocrine and metabolic characteristics at latest clinical follow-up

3.4.1 | Hypopituitarism

Details of individual pituitary hormone deficiency, anterior panhypopituitarism and cranial diabetes insipidus at latest clinic follow-up are demonstrated in Table 2. The incidence of GH, gonadotrophins and ACTH deficiencies improved over the course duration of the study. Anterior panhypopituitarism was recorded in 113 patients (113/138; 82%) with no difference found between COCP (42/47; 89%) and AOCP (71/91; 78%) ($P = .1$). Anterior panhypopituitarism was similar in those treated with surgery only (43/55; 78%) compared to those who had surgery and radiotherapy (68/79; 86%) ($P = .23$) (Table S1). Anterior panhypopituitarism improved during the course time of the study from 82% in quartile one to 63% in quartile four (Table 2) (Figure 4). Cranial diabetes insipidus occurred in 87 patients (87/139; 63%). There was no association in cranial diabetes insipidus between COCP (32/47; 67%) and AOCP (55/92; 60%) ($P = .29$), and no significant difference was observed among all quartiles ($P = .27$) (Table 2).

3.4.2 | Metabolic parameters

BMI data were available for 105 patients of COCP and AOCP. Overall, 88 patients (88/105; 84%) had raised BMI over 25 kg/m$^2$, 35 patients (35/44; 80%) had COCP, and 53 patients (53/61; 86%) had AOCP with no significant difference in prevalence of obesity between the two groups ($P = .31$). The median BMI was 29.2 kg/m$^2$ (IQR 25.5-34.6 kg/m$^2$). Only 17 patients (17/105; 16%) of both age of onset groups maintained normal weight (BMI 18.5 and 24.9 kg/m$^2$); more than one-third (37/105; 35%) were overweight (BMI 25 to 29.9 kg/m$^2$), and approximately a quarter of patients had class I obesity (BMI 30.0 to 34.9 kg/m$^2$) (27/105; 26%), whereas class II (BMI 35.0 to 39.9 kg/m$^2$) and class III obesity (BMI equal to or greater than 40.0 kg/m$^2$) were less prevalent in this cohort (11/105; 11% and 13/105; 12%), respectively. High BMI ($\geq$25 kg/m$^2$) was not associated with the mode of surgery (TSS vs TCS) ($P = .57$) and the age group at onset ($P = .31$). Higher BMI ($\geq$25 kg/m$^2$) was noted in those received radiotherapy (61/67; 91%) than those treated with surgery only (26/37; 70%) ($P = .006$). The median BMI for those received postoperative radiotherapy was 30.6 kg/m$^2$ and for those treated with surgery only was 25.9 kg/m$^2$. There was no significant difference in the incidence of raised BMI ($\geq$25 kg/m$^2$) among all quartiles during the time course of the study ($P = .14$; Table 2).

Data for hyperlipidaemia and hypertension were available for 136 patients. Thirty-three patients of both age groups at onset (33/136; 24%) were prescribed lipid-lowering agents, 8 COCP (8/47; 17%) and 25 AOCP (25/89; 28%) with no significant difference between the two groups ($P = .15$). The temporal trend for the use of lipid-lowering agents was not significant across the four quartiles ($P = .41$). Twenty-three patients of COCP and AOCP (23/136; 17%) were receiving antihypertensives, 5 COCP (5/47; 11%) and 18 AOCP (18/89; 20%) with no significant difference between the two groups ($P = .16$). The trend of antihypertensive therapy over the course of the study was not significant ($P = .15$). Data for antidiabetic therapy were available for 134 patients, 19 patients (19/134; 14%) from both age of onset groups required antidiabetic therapy, 3 COCP (3/48; 6%) and 16 AOCP (16/86; 18%). The incidence of type two diabetes mellitus was associated with age of onset ($P = .04$), but the overall incidence of type two diabetes mellitus among quartiles did not differ ($P = .67$).

4 | DISCUSSION

In this large UK multicentre study of craniopharyngioma, with a long duration of follow-up, we have demonstrated a significant temporal trend in favour of less long-term hypopituitarism. This suggests that modern management techniques of both COCP and AOCP are associated with greater preservation of pituitary hormone reserve. At last clinical review, anterior panhypopituitarism affected 82%, while 63% suffered cranial diabetes insipidus. This is in line with other reported data reporting the endocrine impact of craniopharyngioma.12-15 Wijnen et al12 reported higher frequency of secondary hypogonadism at 92% in 128 patients after a median follow-up of 13 years. In addition, they observed a higher rate of anterior panhypopituitarism and cranial diabetes insipidus in COCP than AOCP. Lo AC et al10 observed lower rate of GH and gonadotrophin deficiency in 123 patients at 47% and 55%, respectively, during a median follow-up of 8.9 years. However, these studies did not analyse the temporal trend in patient outcomes as well as refinements in endocrine
HUSSEIN E t al. parable with other studies. Timing of cranial irradiation post-
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surgery remains controversial.

There may be reluctance to offer prophylactic radiotherapy than those treated with surgery only. Other studies reported this outcome involved smaller number of patients with shorter follow-up duration when compared to this series. The temporal trend in the use of radiotherapy was not different across the quartiles when compared to surgical technique. The administration of radiotherapy was not influenced by the route of surgery (TSS vs TCS). One of the important limitations here is the lack of detailed data of preoperative tumour size and immediate postsurgical tumour volume reduction which may be an important influencing factor. These data were not consistently available for this cohort and were therefore not included in the analysis.

Direct hypothalamic invasion or damage secondary to surgery/ radiotherapy is associated with adverse metabolic and cardiovascu-
ar morbidities. Disruption of the regulatory centres in the hypo-
thalamus alters physical tolerance, bodily energy consumption and satiety. Consequently, craniopharyngioma patients may develop hypothalamic obesity and metabolic syndrome. Excess weight is prevalent in up to 19% in COCP at presentation, with higher obesity rates of 30%-55% after successful therapy despite adequate hormone replacement. In our series, obesity (BMI ≥ 30 kg/m²) occurred in 49% of those who had BMI data available which is in agreement with other studies.

TABLE 2 The incidence of individual pituitary hormone deficiency, anterior panhypopituitarism, cranial diabetes insipidus and BMI (≥ 25 kg/m²) of the full cohort at latest clinical follow-up across all four quartiles

<table>
<thead>
<tr>
<th></th>
<th>Total number</th>
<th>Qtr1</th>
<th>Qtr2</th>
<th>Qtr3</th>
<th>Qtr4</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH</td>
<td>119/135 (88%)</td>
<td>34/35 (97%)</td>
<td>31/34 (91%)</td>
<td>31/33 (94%)</td>
<td>23/33 (70%)</td>
<td>.001</td>
</tr>
<tr>
<td>FSH/LH</td>
<td>99/121 (81%)</td>
<td>28/30 (93%)</td>
<td>25/30 (83%)</td>
<td>24/29 (83%)</td>
<td>22/33 (67%)</td>
<td>.01</td>
</tr>
<tr>
<td>ACTH</td>
<td>116/141 (82%)</td>
<td>31/35 (89%)</td>
<td>30/35 (86%)</td>
<td>31/35 (88%)</td>
<td>24/36 (67%)</td>
<td>.03</td>
</tr>
<tr>
<td>TSH</td>
<td>119/139 (86%)</td>
<td>31/35 (89%)</td>
<td>31/35 (89%)</td>
<td>32/36 (89%)</td>
<td>25/34 (74%)</td>
<td>.1</td>
</tr>
<tr>
<td>APH</td>
<td>113/138 (82%)</td>
<td>31/35 (88%)</td>
<td>30/34 (88%)</td>
<td>31/34 (91%)</td>
<td>21/35 (63%)</td>
<td>.004</td>
</tr>
<tr>
<td>Cranial DI</td>
<td>87/139 (63%)</td>
<td>22/35 (63%)</td>
<td>27/33 (82%)</td>
<td>19/35 (54%)</td>
<td>20/35 (57%)</td>
<td>.3</td>
</tr>
<tr>
<td>BMI (≥ 25 kg/m²)</td>
<td>88/105 (84%)</td>
<td>19/26 (73%)</td>
<td>27/31 (87%)</td>
<td>24/28 (85%)</td>
<td>18/20 (90%)</td>
<td>.14</td>
</tr>
</tbody>
</table>

Abbreviations: ACTH, adrenocorticotropic hormone; APH, anterior panhypopituitarism; BMI, body mass index; DI, diabetes insipidus; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; Qtr, quartile; TSH, thyroid-stimulating hormone.

FIGURE 4 The trend of anterior panhypopituitarism at latest clinical review in the full cohort. The dark bars represent patients with panhypopituitarism, while grey bars represent those with no panhypopituitarism. Qtr, quartile

Care over a prolonged period. We did not detect a significant difference in anterior panhypopituitarism between those who underwent surgery only and those received combined surgery and radiotherapy. Length of follow-up postradiotherapy for quartile four ranged between 1 and 5 years. Notably, this was significantly shorter than for other quartiles and this may have contributed to the lower observed rates of hypopituitarism. A previous study of pituitary tumour pa-
tients receiving radiotherapy with follow-up for up to ten years re-
ported that most GH and gonadotrophin deficiency occurred within five years following radiotherapy. There was a lower incidence of GH and gonadotrophin deficiency in quartile four (Table 2); this may represent a trend towards less hypopituitarism.

Radiotherapy and radiosurgery are increasingly relied upon to prevent and treat tumour recurrence and regrowth in craniopharyngioma. More than two-thirds of patients in this cohort received radiotherapy to provide tumour control which is comparable with other studies. Timing of cranial irradiation post-
surgery remains controversial. There may be reluctance to offer immediate postoperative radiotherapy because of the potential risk of long-term neurovascular consequences and secondary malignancy especially in children and young adults. However, others support the administration of early radiotherapy to control tumour progression after resection to avoid further surgical interven-
tion. Several studies demonstrated no significant difference in progression-free survival after early postoperative versus late radiotherapy for tumour regrowth. In contrast, others found fewer craniopharyngioma relapse with early radiotherapy given as initial therapy when compared with those received late radiother-

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Pharyngioma. More than two-thirds of patients in this cohort received radiotherapy to prevent and treat tumour recurrence and regrowth in craniosurgery. There may be reluctance to offer immediate postoperative radiotherapy than those treated with surgery only. Other studies reported this outcome involved smaller number of patients with shorter follow-up duration when compared to this series. The temporal trend in the use of radiotherapy was not different across the quartiles when compared to surgical technique. The administration of radiotherapy was not influenced by the route of surgery (TSS vs TCS). One of the important limitations here is the lack of detailed data of preoperative tumour size and immediate postsurgical tumour volume reduction which may be an important influencing factor. These data were not consistently available for this cohort and were therefore not included in the analysis.

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thalamus alters physical tolerance, bodily energy consumption and satiety. Consequently, craniopharyngioma patients may develop hypothalamic obesity and metabolic syndrome. Excess weight is prevalent in up to 19% in COCP at presentation, with higher obesity rates of 30%-55% after successful therapy despite adequate hormone replacement. In our series, obesity (BMI ≥ 30 kg/m²) occurred in 49% of those who had BMI data available which is in agreement with other studies. Those who received radiotherapy had a higher BMI than those treated with surgery only. This might be attributed to the possibility of presentation with larger, more invasive tumours in this group prior to radiotherapy. Lustig et al. noted hypothalamic irradiation of greater than 51 Gy was an independent
risk factor for developing obesity in children who had received cranial irradiation for different brain tumours, and this effect was observed even after excluding patients with hypothalamic/thalamic tumours.

Patients with pituitary dysfunction have higher rates of cardiovascular complications and premature mortality when compared to the general population. A high prevalence of hyperlipidaemia, hypertension and insulin resistance are possible contributors. In this cohort, we identified the diagnoses of dyslipidaemia, hypertension and type two diabetes mellitus by therapy. However, we acknowledge that there may be differences in thresholds in treating cardiovascular risk factors in pituitary patients in different settings, with no clear evidence-based guidance. Consequently, patients defined as having increased cardiovascular risk might differ across centres and quartiles and indeed the results from our cohort are likely to under-represent the true occurrence of these risk factors in such patients. In addition, the lack of detailed hormones deficiencies data at presentation for most of the patients might bias metabolic outcomes in this cohort.

Since this study relied on recruiting patients at latest clinical review, this possibly introduced a selection bias caused by an uncertain number of patients who had been lost to follow-up or died. This may have particularly affected the quartiles treated at early stages of the study period and therefore this could potentially have introduced some bias. Defining hormone deficiency based on replacement therapy is of course less robust than analysing endocrine results prior to replacement; however, the nature of the study, with such a long follow-up across multiple centres/laboratories, would have made this very difficult.

The data extraction was based on retrospective review of medical records and hence is subjective to inherent limitations of retrospective studies. Other limitations include the lack of complete data of preoperative tumour size and the extent of surgical excision. The potential bias of different follow-up duration across quartiles should be taken into consideration. Statistical analysis used to calculate the trend in all four quartiles was invariably significantly influenced by the change from quartile three to quartile four. In addition, the histological data in this series are limited which precludes meaningful conclusion of craniopharyngioma regrowth. However, our study included a large number of craniopharyngioma patients with childhood and adult onset, despite the rarity of the condition, with long median follow-up duration. It highlights the extent of long-term endocrine complications in craniopharyngioma particularly obesity rate, hypertension and type two diabetes mellitus.

In conclusion, craniopharyngioma is associated with substantial endocrine-related morbidities. The incidence of panhypopituitarism reduced significantly with the advent of new surgical techniques, notably TSS. The role of immediate radiotherapy postresection remains controversial. Craniopharyngioma survivors require lifelong follow-up and mandate multidisciplinary expertise to optimize overall outcome.

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CONFLICT OF INTEREST
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DATA AVAILABILITY STATEMENT
The data that support the findings of this study are openly available at https://doi.org/10.5522/04/12023025.v1

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