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The development of hypothalamic obesity in craniopharyngioma patients: A risk factor analysis in a well-defined cohort

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Abstract

Background: Hypothalamic obesity (HO) is a major concern in patients treated for craniopharyngioma (CP). The influence of degree of resection on development of HO, event-free survival (EFS), and neuroendocrine sequelae is an issue of debate.

Procedure: A retrospective cohort consisting of all CP patients treated between 2002 and 2012 in two university hospitals was identified. Multivariable logistic regression was used to study the associations between preoperative BMI, age at diagnosis, tumor volume, performed surgical resection, and presence of HO at follow-up.

Results: Thirty-five patients (21 children and 14 adults) were included. Median follow-up time was 35.6 months (4.1–114.7). Four patients were obese at diagnosis. HO was present in 19 (54.3%) patients at last follow-up of whom eight were morbidly obese. Thirteen (37.1%) patients underwent partial resection (PR) and 22 (62.9%) gross total resection (GTR). GTR was related to HO (OR 9.19, 95% CI 1.43–59.01), but for *morbid* HO, obesity at diagnosis was the only risk factor (OR 12.92, 95% CI 1.05–158.73). EFS in patients after GTR was 86%, compared to 42% after PR (log-rank 9.2, $P = 0.003$). Adjuvant radiotherapy after PR improved EFS (log-rank 8.2, $P = 0.004$). Panhypopituitarism, present in 15 patients, was mainly seen after GTR.

Abbreviations: ACTHD, adrenocorticotropic hormone deficiency; BMI, body mass index; CDI, central diabetes insipidus; CP, craniopharyngioma; EFS, event-free survival; GH, growth hormone; GHD, growth hormone deficiency; GTR, gross total resection; HO, hypothalamic obesity; MR, magnetic resonance; OR, odds ratio; PR, partial resection; QoL, quality of life; TSHD, thyroid-stimulating hormone deficiency.

Conclusions: HO is less frequent after PR than after GTR, but PR cannot always prevent the development of morbid obesity in patients with obesity at diagnosis. PR reduces the occurrence of panhypopituitarism. When developing a treatment algorithm, all these factors should be considered.

KEYWORDS
craniopharyngioma, hypothalamic diseases, neurosurgery, obesity

1 | INTRODUCTION

Craniopharyngioma (CP) is a rare tumor, with a bimodal distribution in children (5–14 years) and adults (50–74 years).[1] Histologically this tumor is benign (WHO grade I) with the adamantinomatous histology more frequently seen in the younger patients and the papillary subtype in adult and elderly patients.[2] Despite its benign histological characteristics, CP may cause severe morbidity, due to its close anatomical relation with the optic chiasm, pituitary gland, and hypothalamus. One of the most important long-term adverse effects is hypothalamic obesity (HO), which has a major negative impact on health, quality of life (QoL), and self-esteem.[3,4] Although HO may be present at diagnosis, it is not the most frequent presenting symptom with a prevalence varying between 4 and 15%.[5] After treatment, HO becomes more common, especially in children, with a prevalence up to 55%.[6] Consequences of severe HO include an increased risk of developing metabolic syndrome, cardiovascular disease, respiratory problems, psychosocial complications, and excess mortality.[7–9]

Obesity in patients with CP is ascribed to hypothalamic dysfunction, leading to hyperphagia, decreased resting energy expenditure, insulin resistance, and a distorted day-night rhythm, resulting in daytime somnolence and decreased activity. An additional factor in the development of HO is acquired hypopituitarism, for which adequate timing and dosing of growth hormone, thyroxine, glucocorticoids, and sex steroid treatment is essential.[10,11]

One of the risk factors for HO at follow-up is the degree of hypothalamic involvement at time of diagnosis.[3,12–16] Also, higher preoperative body mass index (BMI),[17] younger age at diagnosis,[8,9] and extent of surgery have been observed to play a role in the development of HO.[18,19]

At present, pharmacotherapeutic options for HO are limited. Bariatric surgical procedures, such as Roux-en-Y gastric bypass, may be a promising treatment for HO, but it requires an irreversible surgical procedure that is not preferable in young patients with CP.[20,21] Therefore, prevention of HO is of primary importance. In the literature, partial resection (PR) has been proposed to reduce HO by limiting hypothalamic damage.[18] Risk-based treatment algorithms have been proposed to select subgroups in which PR may be beneficial.[22,23] To provide more data for these treatment algorithms, the aim of this study was to define the influence of gross total resection (GTR) versus PR on the development of HO and morbid HO in a well-defined cohort during a 10-year period. Second, we analyzed the influence of GTR versus PR on event-free survival (EFS) and neuroendocrine sequelae.

2 | METHODS

2.1 | Patients

All children (i.e., age at CP diagnosis ≤18.0 years) and adults diagnosed with CP (including one case suspected of CP with the final diagnosis of sellar xanthogranuloma at pathology) in two university medical centers in the Netherlands between January 2002 and May 2012 were evaluated for potential inclusion (n = 41). Of six patients, auxological data could not be retrieved and therefore they were excluded from further analyses.

2.2 | Ethics

The medical ethical board of the Academic Medical Center considered the retrospective approach of our study to be within the regulations of the Dutch Medical Research Involving Human Subjects Act, with no requirement to retrieve informed consent from patients or parents.

2.3 | Study information

All charts were reviewed for auxological data (age, gender, height, and weight) and presenting symptoms, including symptoms of hypothalamic damage, endocrine deficits, as well as visual impairment. Information about immediate (cyst) drainage for relief of intracranial pressure, intended and performed surgery (GTR vs. PR vs. biopsy), and the initial surgical approach (transcranial vs. transsphenoidal) were retrieved. Presence of residual disease or recurrence, subsequent surgery, and postoperative radiotherapy (either adjuvant or in case of tumor progression as salvage therapy) were extracted from the medical charts. At last follow-up, the patients were judged as having no evidence of disease or stable disease depending on the presence of residual tumor on last performed postoperative magnetic resonance imaging (MRI) or as disease-related death in case the patient died during follow-up. Data were collected at the time of initial presentation, postoperatively, and at the last follow-up contact.

2.4 | Evaluation of magnetic resonance images

Preoperative and postoperative magnetic resonance (MR) scans after the initial surgical intervention or in case of recurrence or progression of the disease, also the MR scan after the second surgical intervention, were reviewed independently by two experienced neuroradiologists, who were blinded for the clinical outcome of patients and for each other's scoring results. Both radiologists scored the following items: preoperative presence of hydrocephalus, hypothalamic edema,

and the degree of hypothalamic involvement. Hypothalamic involvement was graded according to the Paris grading system:[16] no hypothalamic involvement (grade 0), tumor abutting or displacing the hypothalamus, or pushing against the bottom of the third ventricle (grade 1), and severe hypothalamic involvement or unidentifiable hypothalamus (grade 2). Postoperative hypothalamic damage was graded as no hypothalamic damage (grade 0), negligible hypothalamic damage or residual tumor displacing the hypothalamus (grade 1), and significant hypothalamic damage in which the floor of the third ventricle is no longer identifiable (grade 2). The grading system for assessment of the hypothalamic involvement of the CP was discussed with each radiologist separately, but was not discussed in advance between the radiologists themselves. Interobserver agreement for hypothalamic involvement, which could be assessed in 32 patients, was 0.27 (Cohen's kappa) for the preoperative assessment. For the postoperative assessment of hypothalamic involvement, performed in 30 available MR scans, the interobserver agreement was 0.36. Because of the low interobserver agreement, the Paris grading was excluded from (multivariable) analysis. The presence of obesity at diagnosis was therefore used as a surrogate marker for preoperative hypothalamic involvement in multivariable analysis. The tumor was measured in three directions: anterior-posterior (a), transverse (b), and craniocaudal (c), and tumor volume was estimated based on the maximal tumor diameters in these three dimensions ($a \times b \times c/2$).

Postoperatively, the degree of resection was graded radiologically as biopsy if <10% was resected, GTR if all visible tumor was resected on postoperative MRI, and all others as PR. Interobserver agreement for the degree of resection was considered as substantial (Cohen's kappa 0.64).[24]

2.5 | Weight parameters

For pediatric patients, SD scores for BMI were calculated to allow comparison with children of the same age and gender.[25] In pediatric patients, obesity was defined as a BMI > 2 SD above the population reference value. In adult patients, obesity was defined as a BMI > 30 kg/m^2.[26] A subgroup analysis was done for patients with morbid obesity, defined as a BMI > 3 SD for children, and >40 kg/m^2 for adults.

2.6 | Endocrine evaluation

Pre- and postoperative endocrine evaluations were collected, including all endocrine diagnoses as documented by the treating physician, and all endocrine basal and dynamic tests that had been performed. For analysis of the presence of pituitary disorders, the diagnoses were defined as present when stated as such by the treating physician, using the normative values of their own hospital's laboratory. In addition, the use and timing of endocrine replacement treatment were scored. Panhypopituitarism was defined as present when all anterior pituitary deficiencies were diagnosed in one patient (i.e., growth hormone deficiency [GHD], thyroid-stimulating hormone deficiency [TSHD], and adrenocorticotropic hormone deficiency [ACTHD], and late puberty in children or hypogonadism in adults).

2.7 | Statistical analysis

Statistical analyses were performed using SPSS (version 23.0, Chicago, IL). Significance levels for all analyses were set at $P < 0.05$. Data are presented as median (range) for continuous data or N (proportion in %) for categorical variables. Obesity, morbid obesity, and age (child versus adult) were analyzed as dichotomous variables. Categorical data were compared using the χ^2 test or a Fisher's exact test where appropriate. Continuous data were compared using the Mann–Whitney U test. Simple logistic regression analysis was used to explore the association between the initial operation and recurrence or progression of CP. Multiple logistic regression analyses were performed to identify predictors for HO and morbid HO, including the variables we considered most relevant: preoperative age, tumor volume and the presence of obesity, and degree of resection (GTR vs. PR or biopsy). The 3-year EFS was assessed by the Kaplan–Meier method. We evaluated the effects of surgical intervention and timing of radiotherapy in these curves as well. Survival curves were compared using the log rank test. For multivariable logistic regression and Kaplan–Meier analyses, children and adults are analyzed as one cohort to expand possibilities for proper risk factor and survival analyses.

3 | RESULTS

3.1 | Patients

Thirty-five patients formed the study cohort, consisting of 21 children and 14 adults (Supplementary Figure S1). Patient characteristics are presented in Table 1. Median follow-up time of the study cohort was 35.6 months (4.1–114.7) after diagnosis. At last follow-up, 23 (65.7%) patients had no evidence of disease and 11 (31.4%) patients had stable disease. One adult patient had died from tumor progression.

3.2 | Patient characteristics

The most common presenting symptoms are summarized in Table 1. Visual impairment was more common in adults ($P = 0.03$), while endocrine deficiencies, especially GHD, were more frequently diagnosed in children ($P = 0.04$). Obesity at diagnosis was present in four patients, of whom two children (5.6 and 14.7 years) and two adults (52.8 and 57.0 years). None of these four obese patients had been diagnosed with an endocrine deficiency at time of CP diagnosis, although both children were suspected for GHD as they showed a decline in height at presentation. Two of the four obese patients had hydrocephalus at diagnosis. In one of the 35 patients, weight parameters could not be retrieved at time of diagnosis. Fifteen (42.9%) patients had been diagnosed with one or more pituitary disorders at diagnosis (Table 1), of whom one had panhypopituitarism.

3.3 | Radiological features

Preoperative imaging, available in 32 patients, showed hypothalamic edema in 12 patients (37.5%) and hydrocephalus in 10 (31.3%). No

TABLE 1 Differences in demographics and clinical characteristics between pediatric and adult craniopharyngioma patients

Characteristic	Children (N = 21)		Adults (N = 14)		*P*-value
	No.	%	No.	%	
Gender					
Male	7	33	8	57	0.16
Age at diagnosis					
Median (range)	9.7 (4.0–15.1)		42.1 (18.4–68.0)		n.a.
Weight and height parameters at diagnosis[a]					
Median weight (SDS)	−1.1 (−3.7 to 4.0)				n.a.
Median height (SDS)	−1.8 (−3.4 to 1.0)				n.a.
Median BMI (SDS or kg/m^2)	0.5 (−2.7 to 5.2)		25.6 (18.9–39.0)		n.a.
Symptoms at diagnosis					
Visual impairment	12	57	13	93	0.03*
Headaches	15	71	9	64	0.72
Weight gain	4	19	4	29	0.69
Obesity (n = 34)[b]	2	10	2	14	1.00
Endocrine deficiency at diagnosis	12	57	3	21	0.04*
Growth hormone deficiency	12		0		0.002*
Central hypothyroidism	3		2		1.00
Central hypocortisolism	1		0		1.00
Pubertal delay/hypogonadism	4		1		0.64
Central precocious puberty	0		n.a.		n.a.
Central diabetes insipidus	0		0		n.a.
Preoperative radiological features (n = 32)					
Hydrocephalus	7	37	3	23	0.47
Hypothalamic edema	6	30	6	50	0.29
Median tumor volume (cm^3)[c]	10.8 (2.0–320.0)		11.1 (1.0–40.0)		0.61
Surgical resection[d]					0.57
Partial resection	7	33	6	43	
Gross total resection	14	67	8	57	
Radiotherapy					
Adjuvant after first surgical resection	4	19	1	7	0.63
At relapse	4	19	3	21	1.00
Total	8	38	4	29	0.72
Recurrence					0.47
Yes	5	24	5	36	
Endocrine deficiency at last follow-up	19	91	13	93	1.00
Growth hormone deficiency	18		7		0.06
Central hypothyroidism	18		12		1.00
Central hypocortisolism	16		10		1.00
Pubertal delay/hypogonadism	11		10		0.13
Central precocious puberty	0		n.a.		n.a.
Central diabetes insipidus	17		9		0.68

*Significant *P*-value.
n.a., not applicable.
[a]For pediatric patients, standard deviation scores (SDS) for height, weight, and BMI scores were calculated to allow comparison with children of the same age and gender. For adult patients, BMI was calculated as kg/m^2.
[b]In one patient, weight parameters at diagnosis could not be retrieved.
[c]The tumor was measured in three directions: anterior–posterior (a), transverse (b), and craniocaudal (c) and median tumor volume was estimated based on the maximal tumor diameters in these three dimensions ($a \times b \times c/2$).
[d]The surgical resection was graded radiologically as biopsy if <10% was resected, gross total resection if all visible tumor was resected, and all others as partial resection. For this analysis, all biopsies (n = 3) were included in the partial resection group.

significant differences in radiological features were found between pediatric and adult patients.

3.4 | Treatment strategy and outcome

Three patients needed emergency drainage to relieve increased intracranial pressure and in two patients drainage of a cyst was performed prior to surgical resection. Of 32 patients with available data about intended surgery, radical resection was proposed in 28 patients (87.5%), a limited resection in two (6.3%) patients, and biopsy or drainage of cyst in one (3.1%) patient, respectively (Supplementary Figure S1). The surgical approach was transcranial in 28 (80.0%) patients and transsphenoidal in seven (20.0%) patients. There were no differences in outcome regarding HO, or recurrence or progression of residual disease between the patients who underwent transsphenoidal or transcranial surgery ($P = 1.00$ and $P = 0.16$, respectively).

On postoperative MR scans of the initial surgery, the result was GTR in 21 (60.0%) patients, PR in 11 (31.4%) patients, and biopsy in three (8.6%) patients. Five of the 14 patients who underwent PR or biopsy were directly treated with adjuvant radiotherapy (50–54 Gy). One patient, initially treated with PR, had GTR at progression of disease 5 months later. Intended surgery, performed surgery, or surgical approach did not differ significantly between pediatric and adult patients.

3.5 | Hypothalamic obesity

At the last follow-up contact, HO was present in 19 (54.3%) patients, of whom eight had morbid obesity. In pediatric patients, HO was more common than in adult patients (66.7% vs. 35.7%, respectively), although the difference did not reach statistical significance ($P = 0.07$). Of the 31 patients without HO at diagnosis, three developed HO after PR (two children, one adult) and 13 after GTR (10 children and one adult) at follow-up. Multivariable logistic regression analysis showed that the presence of obesity at the last follow-up contact was significantly related to GTR (odds ratio [OR] 9.19, 95% CI 1.43–59.01, Table 2).

3.6 | Morbid obesity

At the last moment of follow-up, morbid HO was present in eight patients, five of whom were children. Three of these eight patients (two children and one adult) were already obese at diagnosis. For the presence of morbid HO at last follow-up, obesity at diagnosis was a significant risk factor in multivariable analyses (OR 12.92, 95% CI 1.05–158.73), but GTR was not (OR 2.00, 95% CI 0.27–14.75, Table 2). Six of the eight patients with morbid HO at last follow-up had undergone a GTR and two patients a PR. One of the patients with PR was already obese at diagnosis. All eight morbid patients developed TSHD, ACTHD, and central diabetes insipidus (CDI) postoperatively. Seven patients developed GHD and four hypogonadism.

3.7 | Recurrence, progression, and EFS

Ten patients had a recurrence, or progression of residual disease, of whom two after complete resection and eight after PR or biopsy. The median time to recurrence, or growth of residue, was 8.6 months (0.9–33.2) after the initial operation. At recurrence or progression, patients underwent a second surgical resection (n = 5) and/or received radiotherapy (n = 7, 12.5–54 Gy).

PR or biopsy was a significant risk factor for recurrence or progression of the disease (OR 12.7, $P = 0.006$, 95% CI 2.09–76.70). For patients with a GTR, the EFS was 86%, compared to 42% after PR or biopsy (log-rank 9.2, $P = 0.003$) (Figure 1A). Of the patients who received adjuvant radiotherapy after PR or biopsy, none showed progression of the disease, while eight out of nine patients who did not receive adjuvant radiotherapy after PR or biopsy showed progression of disease (log-rank 8.2, $P = 0.004$) (Figure 1B). The EFS after GTR was similar to that after PR with adjuvant radiotherapy (log-rank 0.6, $P = 0.43$). Radiotherapy, either adjuvant or as salvage therapy, did not influence the presence of HO at follow-up ($P = 0.28$, $P = 0.64$, and $P = 0.68$ respectively), nor did the development of recurrence, or progression of residual disease, at follow-up ($P = 0.45$).

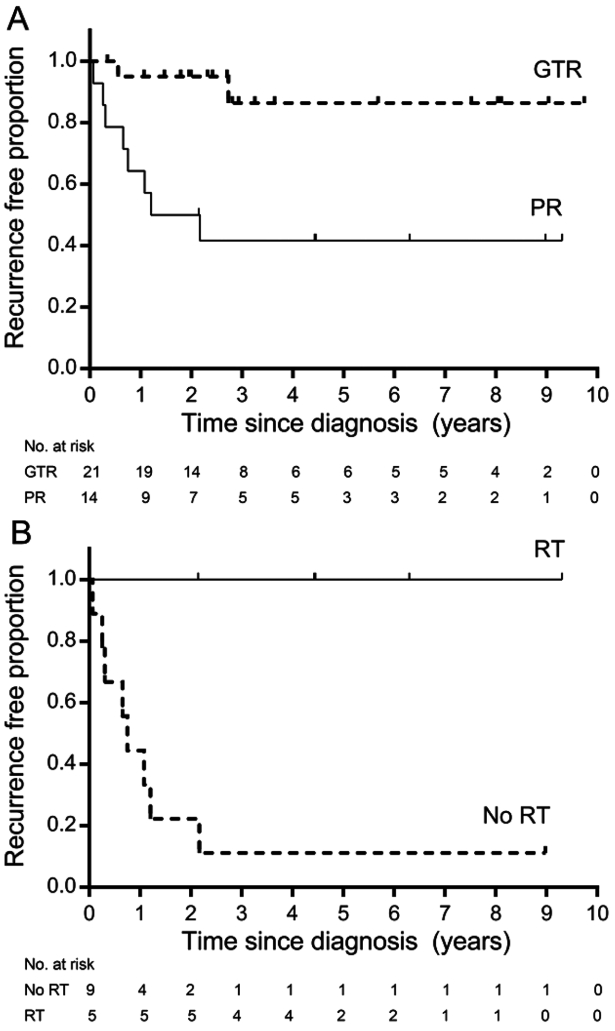

FIGURE 1 (A and B) Recurrence-free proportion of patients who underwent a gross total resection (GTR) versus partial resection (PR) or biopsy (upper graph) and of patients who received adjuvant radiotherapy (RT) after partial resection or biopsy versus no adjuvant RT (lower graph)

TABLE 2 Risk factors associated with hypothalamic obesity at last follow-up in multivariable analysis (N = 35)

Covariate	Obesity (N = 19) OR (95% CI)	Morbid obesity (N = 8) OR (95% CI)
Age at diagnosis		
Child	5.41 (0.81–36.31)	1.47 (0.21–10.30)
Obesity at diagnosis		
Yes	1.92 (0.15–24.58)	12.92 (1.05–158.73)*
Tumor volume (cm^3)	1.01 (0.99–1.02)	1.00 (0.98–1.02)
Surgical resection		
Gross total resection	9.19 (1.43–59.01)*	2.00 (0.27–14.75)

*Significant OR.
OR, odds ratio; CI, confidence interval.

3.8 | Endocrine outcome

At the last follow-up contact, 32 (91.4%) patients had a pituitary disorder, of whom 15 (42.9%) patients had panhypopituitarism (Table 3).

Of the 25 patients with GHD at follow-up, 13 were diagnosed after surgical resection. Growth hormone (GH) treatment was started in 23 patients, after a median of 0.9 year (range 0.3–3.9) after initial surgery. The time interval between the surgical resection and start of GH treatment, did not differ significantly between children and adults ($P = 0.05$), obese and nonobese patients at last follow-up ($P = 0.55$), patients with PR versus GTR ($P = 0.84$), or between patients who had recurrence or progression of residual disease at follow-up ($P = 0.74$). The presence of GHD did not influence the development of HO at follow-up ($P = 0.14$).

Of the 30 patients with TSHD at follow-up, five had been diagnosed at CP diagnosis, 23 directly postoperatively, and two during follow-up (0.6 and 1.1 years after initial surgical resection, respectively).

Of the 26 patients in whom ACTHD was diagnosed, 23 were diagnosed directly postoperatively, of whom eight were dynamically tested. Of the other three patients, one patient had been diagnosed with ACTHD at diagnosis, and two were diagnosed during follow-up. ACTHD was more frequently present in obese versus nonobese patients; however, this difference was not significant ($P = 0.05$).

Of the 21 patients who developed hypogonadism, five had been diagnosed prior to diagnosis and 16 were diagnosed during follow-up.

CDI developed in 26 patients after the surgical resection, of whom six patients underwent PR and 20 GTR. At last follow-up, 15 patients had panhypopituitarism. Both CDI and panhypopituitarism were more frequently seen in patients who underwent GTR compared to PR (n = 20 and n = 13, respectively; $P = 0.01$). Panhypopituitarism was not related to the presence of HO at follow-up ($P = 0.05$). Radiotherapy, either adjuvant or as salvage therapy, did not influence the presence of panhypopituitarism at follow-up ($P = 0.12$, $P = 1.00$, and $P = 0.20$, respectively).

4 | DISCUSSION

In this well-defined cohort of 35 patients with CP, we confirm that HO is less frequent after PR than after GTR. However, PR does not seem to prevent morbid obesity in all, especially not in patients with obesity at diagnosis. These results point to the existence of a preoperative hypothalamic disorder, which can only partially be influenced by the degree of resection. However, as PR seems to reduce the occurrence of panhypopituitarism and CDI, it still seems beneficial to aim for PR, even when obesity is present at diagnosis. After PR, reduced EFS is seen when compared to GTR, which seems to be overcome with adjuvant radiotherapy. The possible late adverse effects of radiotherapy, not studied in this cohort, must however be taken into account. All these factors should be considered when developing a treatment algorithm for these patients.

Recent studies suggest that it seems reasonable to aim for hypothalamus-sparing surgery, especially in patients with substantial hypothalamic involvement prior to surgery.[18,27] For this reason, we evaluated the influence of preoperative hypothalamic involvement and the extent of surgical resection on the development of HO. Of the different tools developed to assess hypothalamic involvement, the Paris grading is a widely used scoring system.[28] Therefore, we also intended to use the Paris grading in our cohort to define the existence of preoperative hypothalamic involvement. However, because of a low interobserver agreement for preoperative hypothalamic involvement between two well-experienced neuroradiologists, we instead used obesity at diagnosis as surrogate marker of possible preoperative hypothalamic involvement. For future studies, alternative MRI criteria to define hypothalamic involvement, such as tumor extension toward the mammillary bodies, should be considered, and the interobserver variability of scoring systems deserves further attention.[28,29]

For HO in general, GTR is a risk factor, indicating PR may be preferential. The benefit of reducing HO versus the increased recurrence rate after hypothalamus-sparing surgery, however, is still an important issue of debate.[18,30] In our cohort, PR shows a higher recurrence rate, which, when evaluated in more detail, was only seen in the patients who did not receive adjuvant radiotherapy after initial surgery. This might implicate that radiotherapy is favorable after PR; however, we did not study possible negative late effects of adjuvant radiotherapy, such as neurocognitive impairment and the development of meningioma.[31] The role and timing of radiotherapy after PR must be studied in future prospective trials, taking into account the option of direct (stereotactic) radiotherapy after initial surgery, or an initial wait-and-scan policy following initial surgery with adjuvant radiotherapy

TABLE 3 Differences in demographics and clinical characteristics between 35 craniopharyngioma patients with and without obesity at follow-up

	Obesity at follow-up (N = 19)		No obesity at follow-up (N = 16)		
Characteristic	**No.**		**No.**	**%**	***P*-value**
Gender					0.92
Male	8	42	7	44	
Age at diagnosis					0.07
Child	14	74	7	44	
Adult	5	26	9	56	
Symptoms at diagnosis					
Visual impairment	12	63	13	81	0.29
Headaches	13	68	11	69	0.98
Weight gain	7	37	1	6	0.05
Obesity (n = 34)[a]	3	16	1	7	0.61
Endocrine deficiency at diagnosis	8	42	7	44	0.92
Growth hormone deficiency	7		5		0.95
Central hypothyroidism	1		4		0.15
Central hypocortisolism	0		1		0.42
Pubertal delay/hypogonadism	3		2		1.00
Central precocious puberty	0		0		n.a.
Diabetes insipidus	0		0		n.a.
Preoperative radiological features (n = 32)					
Hydrocephalus	6	33	4	29	1.00
Hypothalamic edema	9	47	3	23	0.27
Median tumor volume (cm^3)[b]	12.4 (5–320)		9.2 (1–192)		0.15
Intended surgical resection					0.32
Complete resection	16	84	12	75	
Limited resection	1	5	3	19	
Unknown	2	11	1	6	
Surgical resection[c]					0.03*
Partial resection	4	21	9	56.3	
Gross total resection	15	79	7	44	
Radiotherapy					
Adjuvant after first surgical resection	2	11	3	19	0.64
At relapse	3	16	4	25	0.68
Total	5	26	7	44	0.28
Recurrence					0.45
Yes	4	21	6	38	
Endocrine deficiency at last follow-up	18	95	14	88	0.58
Growth hormone deficiency	16		9		0.14
Central hypothyroidism	18		12		0.16
Central hypocortisolism	17		9		0.05
Pubertal delay/hypogonadism	11		10		0.74
Central precocious puberty	0		0		n.a.
Central diabetes insipidus	17		9		0.10
Panhypopituitarism	11		4		0.05

*Significant *P*-value.
n.a., not applicable.
[a]In one patient, weight parameters at diagnosis could not be retrieved.
[b]The tumor was measured in three directions: anterior–posterior (a), transverse (b), and craniocaudal (c) and median tumor volume was estimated based on the maximal tumor diameters in these three dimensions ($a \times b \times c/2$).
[c]The surgical resection was graded radiologically as biopsy if <10% was resected, gross total resection if all visible tumor was resected and all others as partial resection. For this analysis, all biopsies (n = 3) were included in the partial resection group.

in case of progression.[32] This last option seems to be most favorable, especially in young children. Also, advancements in the field of radiotherapy, such as proton beam therapy, may reduce radiation exposure to healthy tissues, and possibly diminish the occurrence of adverse effects in future CP patients.[33]

Neuroendocrine sequelae are frequently observed in CP patients, either as presenting symptom or as postoperative complication. In our study, postoperative panhypopituitarism was mainly seen in patients who underwent GTR. Recently, in accordance with our findings, it has been demonstrated that conservative surgery may limit neuroendocrine sequelae.[34] The relation between endocrine deficiencies and the development of obesity in childhood cancer survivors has been previously observed. In our cohort, the majority of patients with ACTH deficiency had HO at follow-up, either reflecting the degree of hypothalamic damage or possibly reflecting too high doses of hydrocortisone substitution therapy. Next to high doses of hydrocortisone, suboptimal GH and thyroid hormone replacement therapy may influence BMI. Adequate screening and timely treatment of endocrinopathies might favor the metabolic state, and possibly diminish the degree of obesity. Dynamic testing, especially in case of suspicion of ACTHD, should be considered to reduce overtreatment with steroids.

Several limitations of the study should be noted. First, as this was a retrospective cohort analysis, differences in follow-up time of the individual CP patients were present. This may have possibly influenced the prevalence of endocrine disorders, obesity, and EFS in the patients with the shortest follow-up time. Moreover, due to the retrospective study design, we could not reliably evaluate neuropsychological outcome or quality of survival at follow-up. Second, the cohort was limited due to the rarity of the disease. This is reflected in the sometimes wide confidence intervals of the risk factor analyses. Third, we included both adult and pediatric patients. As histologic subtypes and disease processes differ among different ages, the mix of both age groups made the cohort more heterogeneous. Finally, we used obesity at diagnosis as surrogate marker for hypothalamic involvement, instead of the "gold standard" that is grading on MRI. This was chosen, because the interobserver agreement of both pre- and postoperative hypothalamic involvement based on neuroimaging was too low, making these results unreliable.

Despite these limitations, the results presented here represent outcomes of a well-defined cohort of CP patients, including all auxological and treatment data, MR images, and endocrine data (laboratory measurements, stimulation tests, as well as timing of hormonal treatment). The fact that both adults and children were included in this cohort has empowered the statistical analyses. National registry databases and international collaborations should be encouraged, as these will increase patient numbers and optimize future retrospective and prospective cohort studies.[35]

From this cohort of CP patients with well-documented follow-up data, it seems that the presence of obesity at diagnosis as well as extent of surgical resection, are both related to the development of (morbid) HO later in life. The observation that the development of morbid obesity is strongly related to the presence of obesity at diagnosis indicates preoperative hypothalamic involvement that may not be overcome by limiting the degree of surgical resection. However, as GTR increases the risk of neuroendocrine sequelae at follow-up, aiming for a PR will still be beneficial, even in the obese. Considering all these factors, preoperative risk-based treatment algorithms must be developed, weighing the risk of developing HO in relation to the presence of obesity at diagnosis, the degree of resection, the risk of recurrence, the risk of adverse effects due to adjuvant radiotherapy taking into account the age of the patient, and the development of neuroendocrine sequelae. To prevent morbid HO, patients (and their parents) should be actively counseled preoperatively by the multidisciplinary team about potential change in eating behavior, a reduced metabolic state, and the limited pharmacotherapeutic options for HO. Postoperatively, early involvement of a dietician, psychologist, and physiotherapist may prevent development or further aggravation of HO by providing individual lifestyle and dietary advice, although this can be very challenging in some cases. Regular visits to the outpatient clinic should be offered to closely monitor weight development and to support patients. As HO has a major impact on the QoL in these patients, pre- and postoperative management should be individualized and regularly discussed within the multidisciplinary team.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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SUPPORTING INFORMATION

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