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Citation

Schaik, J. van, Shouten-van Meeteren, A. Y. N., Vos-Kerkhof, E., Janssens, G. O., Porro, G. L., Fiocco, M., ... Santen, H. M. van. (2023). Treatment and outcome of the Dutch childhood craniopharyngioma cohort study: first results after centralization of care. *Neuro-Oncology*, 25(12), 2250-2261. doi:10.1093/neuonc/noad112

Version: Publisher's Version

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Note: To cite this publication please use the final published version (if applicable).

Treatment and outcome of the Dutch Childhood Craniopharyngioma Cohort study: First results after centralization of care

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Abstract

Background. Childhood craniopharyngioma (cCP) has excellent survival, but quality of life may be severely hampered by hypothalamic dysfunction. We aimed to evaluate treatment and hypothalamic outcomes of a Dutch cCP cohort, and evaluate the effect of centralization of care.

Methods. A retrospective cohort study was performed, including cCP patients diagnosed between 2004 and 2021. Treatment characteristics and hypothalamic outcomes were evaluated and compared before and since centralization of care in May 2018.

Results. We included 87 cCP patients. Cyst drainage/fenestration was performed in 29.9%, limited resection in 27.6%, near-total resection in 16.1%, and gross total resection (GTR) in 25.4%. Radiotherapy was given in 46.0%. After a median follow-up of 6.5 years, hypothalamic obesity (HO) was present in 24.7% and panhypopituitarism with diabetes insipidus in 71.3%. Higher body mass index (BMI) SDS at diagnosis and Muller grade II at last magnetic resonance imaging of follow-up were associated with overweight/obesity. No association was found between extensiveness of resection and overweight/obesity at last follow-up. When comparing before and after centralization of care, rates of GTR remained similar, but BMI outcomes changed; mean Δ BMI SDS 1 year after diagnosis from 1.12 (SD 1.15) to 0.81 (SD 1.24), and HO after 1 year decreased from 33.3% to 12.0% ($P = .067$), and after 2 years from 28.6% to 6.7% ($P = \text{NS}$).

Conclusions. In our nationwide cohort, GTR was performed in a relatively low percentage of patients and extensiveness of resection was no longer associated with HO at follow-up. A trend toward improvement of BMI is observed since centralization of care, which needs further exploration.

Key Points

- Extensiveness of resection was no longer associated with overweight/obesity in childhood craniopharyngioma (cCP).
- Significant BMI increase was most prominent in the first year after cCP diagnosis.
- After centralization of care, BMI outcomes seem to improve in cCP.

Childhood craniopharyngioma (cCP) is a rare low-grade tumor, originating in the (supra)sellar region of the brain.¹ Children with cCP commonly present with visual impairment, hypothalamic-pituitary deficiencies, and/or signs of increased

intracranial pressure.^{2–4} Treatment for cCP is multidisciplinary and, in most cases, consists of neurosurgery, radiotherapy (RT), or a combination of both.⁵ Survival of cCP is excellent, with rates up to 92%. Morbidity after treatment, however, can

Importance of the Study

Within this national childhood craniopharyngioma cohort, the frequency of gross total resection was performed in a relatively low percentage of the patients (25.4% of all patients), which is in line with other literature. In addition, extensiveness of resection, with the use of pre-operative radiological assessment of hypothalamic involvement, appeared not to be associated

anymore with hypothalamic obesity (HO). After centralization of care, a trend towards improving BMI outcomes was observed. At last, we found that the increase in BMI SDS was most significant in the first year following surgery with no statistical further increase in the years thereafter, highlighting the need to start HO interventions more early.

be severe, mainly determined by the degree of hypothalamic dysfunction (HD).^{6,7} Currently, there is no effective treatment for HD, except in restoring the hormone levels in panhypopituitarism and to some degree guidance for hypothalamic obesity (HO). HD may result in survivors with morbid obesity and severe behavioral problems.^{5,7} Comparable to alimentary obesity, the cornerstone of HO management is dietary and exercise. Diet may be challenging due to the presence of hyperphagia and for many cCP survivors exercise may be difficult due to the presence of visual acuity or visual field disturbances. For these reason, prevention of hypothalamic damage is one of the most important aims in cCP treatment, including hypothalamus-saving therapeutic approaches that aim to preserve the integrity of nuclei located in posterior hypothalamic areas.⁸

In many studies, gross total resection (GTR) has been shown to be one of the most important risk factors for hypothalamic adverse outcome.^{9–11} Subsequently, rates of GTR have gone down, from 80^{12–14} to 25%,^{11,15–18} and limited resection (LR) is advocated. LR results in more frequent progressive residual disease, for which adjuvant radiotherapy (RT) may be necessary.¹³ LR followed by RT has been shown to have similar tumor control as GTR.¹⁰ However, RT can increase the risk for adverse late events, such as endocrine, vascular, or neurocognitive consequences.¹⁹ The choice for GTR or LR remains a matter of debate and the intended extensiveness of tumor resection may depend on tumor location and pre-operative hypothalamic involvement, for which a grading system has been developed.¹¹ For small cCP with Muller grading 0 or I, a GTR may still be the optimal treatment strategy assuming that the hypothalamic integrity can be preserved. In patients with hypothalamic involvement already present at diagnosis, LR is advocated to decrease tumor mass, merely to release mass effect on the visual pathway, the brain or brain stem, and/or to guarantee CSF flow, while respecting the hypothalamus.²⁰ The complexity in balancing all aspects of this rare disease with risks of serious diverse sequelae requires optimal care by an experienced multidisciplinary team.²¹ Due to the rareness of the disease, from May 2018 onwards, care for cCP in the Netherlands has been largely centralized in the Princess Máxima center for pediatric oncology. In this study, we aimed to evaluate treatment, visual and hypothalamic outcomes in the Dutch cohort of cCP diagnosed between 2004 and 2021. In addition, we aimed to evaluate the effect of centralization of care since May 2018 on treatment and hypothalamic outcomes.

Methods

Study Population

A retrospective cohort study was performed. With the use of PALGA (Pathology databanking and biobanking in The Netherlands) the Dutch cohort of children (≤ 18 years) diagnosed with cCP during the period 2004–2021 was retrieved.²² All children (age ≤ 18 years) diagnosed with cCP between January 2004 and December 2021 with at least 1-year follow-up, known at the Princess Máxima Center, were included. Informed consent was obtained from parents in children <12 years old, from parents and children 12–16 years of age and from children >16 years of age. Given the retrospective character of the data analysis, the local institutional review board decided that the Act on Medical Research Involving Human Subjects did not apply and provided a waiver (20-640/C).

Data Collection

Patient Characteristics

Tumor and treatment-related characteristics, available follow-up data of anthropometric measurements, visual and endocrine parameters were retrospectively collected through chart evaluation until December 2022. Weight (underweight, overweight, or obesity) was classified using the BMI cutoff points per age as defined by Cole et al. 2000.^{23,24}

The upfront surgical procedure (within the first 3 months after cCP diagnosis) was classified into endoscopic cyst drainage/fenestration (eCD/F), LR, near-total resection (NTR), and GTR. Type of resection was based on the report of the neurosurgeon in combination with the report of the radiologist, or if not available, based on the documentation of the treating oncologist. If more than one surgery was performed within the first 3 months with different types of resection, the most invasive type of resection was classified. An endoscopic cyst drainage or fenestration without further resection of tumor tissue reported by the neurosurgeon and/or radiologist, was scored as eCD/F. LR was defined as less than 95% of the tumor resected or a partial resection (with obvious residual tumor mass present) reported by the neurosurgeon and/or radiologist. NTR was defined as more than 95% of the tumor resected, but not all tumor tissue removed. If exact percentages were not reported, NTR was based on neurosurgical and/or radiologist reporting: NTR or reports stating that almost all tumor

was removed and little, minimal, or minor tumor tissue had been left (residual small enhancement lesion but no apparent tumor mass). GTR was defined as having removed all tumor tissue, stated both by the neurosurgeon and radiologist.

Visual Parameters

Data of ophthalmological examination at primary diagnosis and last follow-up were collected. Parameters included best-corrected visual acuity (BCVA), and visual field examination. The BCVA was evaluated monocularly using age-appropriate testing methods. The BCVA measurements were converted into logMAR (Snellen fraction [SF]) values and categorized according to the definitions of visual impairment and blindness based on the International Statistical Classification of Diseases and Related Health Problems, 10th Revision: No or mild visual impairment (BCVA ≤ 0.5 logMAR [SF $\geq 20/70$]), moderate visual impairment (BCVA > 0.5 to 1.0 logMAR [SF $< 20/70$ to $\geq 20/200$]), severe visual impairment (BCVA > 1.0 to 1.3 logMAR [SF $< 20/200$ to $\geq 20/400$]), and blindness (BCVA > 1.3 logMAR [SF $< 20/400$]).²⁵ Visual field examination was performed using age-adapted testing and was scored as impaired if abnormalities (eg, absolute or relative visual field defects) were reported by the ophthalmologist.²⁶ Hemianopsia was present if any type of hemianopsia (homonymous, heteronymous, or quadrantic) was reported.

Score for Clinical Hypothalamic Dysfunction

Presence of clinical HD was scored with data retrieved by retrospective chart review. Severe HD (also referred to as the hypothalamic syndrome), was defined as present or absent, based on the diagnostic criteria of van Santen et al.²⁷ For calculation of this score, the separate domains of HD were scored (hyperphagia, hypophagia, body mass index [BMI], behavioral problems, sleep disorders, temperature regulation disorders, pituitary dysfunction, and radiological Muller grading).

Pituitary Dysfunction

Pituitary dysfunction was defined as present in case of growth hormone deficiency, thyroid-stimulating hormone deficiency, adrenocorticotrophic hormone deficiency (ACTHD), gonadotrophin deficiency (LH/FSHD), central diabetes insipidus (DI), and/or central precocious puberty.

Neuro-Imaging

On the brain magnetic resonance imaging (MRI) was performed at initial diagnosis and at last follow-up, radiological hypothalamic damage was scored using the Muller grading defining grade 0 as no hypothalamic involvement/lesion, grade I as hypothalamic involvement/lesion of the anterior hypothalamus not involving the hypothalamic area beyond mammillary bodies, and grade II as hypothalamic involvement/lesion of the posterior hypothalamic area (with or without involvement/lesion of the anterior hypothalamic area) i.e., involving the area beyond mammillary bodies.¹¹ Hydrocephalus was scored as present if

mentioned in radiology or neurosurgeon report. All items were scored by a trained clinical researcher. If there was uncertainty among the clinical researcher, the scoring was evaluated with the neuro-radiologist and consensus was reached by discussion.²⁸

Tumor Progression

Occurrence of tumor progression or recurrence was defined as present when tumor progression or recurrence was stated on the radiology report or medical chart and treatment for tumor progression/recurrence was given.

Statistical Analysis

Data are presented as mean and standard deviation score (SD) or median [interquartile range] for continuous data, depending on the distribution. Data are presented as percentages for categorical variables. Patients diagnosed $<$ May 2018 were compared to those diagnosed $\geq$ May 2018 (after centralization of care). Between-group differences were evaluated by Student's *t*-test for continuous data with a normal distribution, Mann-Whitney *U* test for continuous data with a skewed distribution, and by χ^2 test or Fisher's exact test for categorical data. To assess violation of normality distribution, QQ plot of the residuals and Shapiro-Wilk's test were employed. Between-group differences were evaluated by one-way analysis of variance (ANOVA) for continuous data with a normal distribution, Kruskal-Wallis test for continuous data with a skewed distribution (skew variables were not further transformed), and by χ^2 test or Fisher's exact test for categorical data. Post hoc testing with Dunnett *t* (2-sided), with the last category as reference was used. BMI SDS measurements were assessed with linear mixed models, using least significant different post hoc testing with correction for multiplicity of testing. To study the effect of possible risk factors on the outcome, univariate and multivariable logistic regression analyses were estimated. Independent variables to be included in the multivariable logistic regression were selected by estimating first the univariate model and by considering the clinical relevance of each variable. $P < .05$ was considered statistically significant. Analyses were performed by using SPSS version 27.0.

Results

In total, 166 children (aged < 18 years) had been diagnosed with cCP in the Netherlands in the period 2004–2021.²² Of these, 105 (63%) were known in the Princess Máxima Center and could be asked for informed consent. In total, 87/105 patients (83%) informed consent was obtained for use of data for this study. Reasons for exclusion were: refusal to participate (10%) and not being able to retrieve for obtaining informed consent/ moved abroad (7%). Of patients diagnosed before May 2018, 48% of the Dutch cohort were included, of patients diagnosed since May 2018, 69% of the cohort were included.

Table 1. Patient Characteristics

Total group (n = 87, 100%)	At diagnosis	At follow-up
Mean age at diagnosis/at FU (years)	7.39 ± 3.67	14.19 ± 4.98
Mean BMI SDS at diagnosis (n = 62)/at FU (n = 85)	0.76 ± 1.52	1.94 ± 1.65
Weight classification at diagnosis(n = 63 ^a)/at FU (n = 85)		
Underweight	1 (1.6)	1 (1.2)
Normal weight	45 (71.4)	37 (43.5)
Overweight	10 (15.9)	26 (30.6)
Obesity	7 (11.1)	21 (24.7)
Muller grading ^b pre-operative (n = 67)/at FU (n = 75) ^c		
Muller 0	2 (3.0)	16 (21.3)
Muller 1	25 (37.3)	20 (26.7)
Muller 2	40 (59.7)	39 (52.0)
Pituitary deficiencies at diagnosis (n = 76)/at FU (n = 87) ^d		
Growth hormone deficiency	26 (34.2)	76 (87.4)
Central hypothyroidism	21 (27.6)	76 (87.4)
Central hypocortisolism	14 (18.4)	66 (75.9)
Hypogonadotropic hypogonadism	1 (1.3)	43 (49.4)
Diabetes insipidus	5 (6.6)	64 (73.6)
Central precocious puberty	0 (0.0)	7 (18.0)
Panhypopituitarism with diabetes insipidus	4 (5.3)	62 (71.3)
No pituitary deficiency	41 (53.9)	8 (9.2)
Visual capacities at diagnosis (n = 42)/at FU (n = 74) ^e		
Normal or mildly decreased visual acuity		
Unilateral per eye	59 (70.2)	112 (75.7)
Bilateral	27 (64.3)	50 (67.6)
Decreased visual acuity (moderate/severe)		
Unilateral per eye	16 (19.0)	20 (13.5)
Bilateral	8 (19.0)	10 (13.5)
Blindness		
Unilateral per eye	9 (10.7)	16 (10.8)
Bilateral	2 (4.8)	2 (2.7)
Visual field impairments (n = 45)/at FU (n = 72)	19 (42.2)	41 (56.9)

FU: Last moment of follow-up.

^aOne patient presented at moment of diagnosis with severe obesity (chart review); however, specific body mass index SDS values were not reported.

^bMuller grading consisting of: grade 0: No hypothalamic involvement/lesion, grade I: Hypothalamic involvement/lesion of the anterior hypothalamus not involving the hypothalamic area beyond mammillary bodies, grade II: Hypothalamic involvement/lesion of the anterior and/or solely posterior hypothalamic area, ie, involving the area beyond mammillary bodies.¹¹

^cNot for all patients magnetic resonance imaging at diagnosis was available.

^dMultiple pituitary deficiencies could be present in one patient. At moment of diagnosis, not for all patients endocrine status was available.

^eNot for all patients visual capacities were available, visual field impairments are lacking in case of young age.

Patient Characteristics at Diagnosis (Table 1)

Table 1 Of all patients included (n = 87), 57.5% were female, mean age at diagnosis was 7.39 years (SD 3.67), and median follow-up time was 6.54 years [IQR 3.11 – 10.69]. Most presenting symptoms were headache (50%) and visual acuity/visual field impairments (38%). Of all patients, 47.4% had hydrocephalus at time of diagnosis (of which 27.8%

received cerebrospinal fluid shunting), while 33.3% presented with papil-edema. Pituitary deficiencies at diagnosis were present in 44.7% and 27% had overweight or obesity. In 23.8%, moderate or severe loss of visual acuity or blindness of both eyes was present. Visual field impairments (either absolute or relative visual field defects) were present at diagnosis in 42.2% of the patients, of which 52.6% of defects consisted of a type of hemianopsia.

cCP Treatment Over the Years

The upfront surgical procedure (within the first 3 months after cCP diagnosis) consisted of eCD/F in 29.9%, LR in 27.6%, NTR in 16.1%, and GTR in 25.3%. Median follow-up time was 6.54 years [IQR 3.11–10.69]. At last follow-up, the most extensive resection given was eCD/F at 12.6%, LR at 29.9%, NTR at 21.8%, and GTR at 34.5%. The median number of surgeries was 2 [range 0–6]. In one patient, a wait-and-see policy was chosen and no surgical treatment has been necessary. Interferon alpha for cystic cCP was given in 11.5% as initial therapy, and in 6.9% during follow-up at time of cyst growth. In 8.0% of local (conventional or proton) RT immediately after first surgery was given, and 37.9% received RT at time of progression/recurrence after a median follow-up time of 2.07 years [IQR 1.00–3.79] after cCP diagnosis. When compared to children diagnosed before May 2018 ($n = 62$), children diagnosed since May 2018 ($n = 25$) had similar rates of eCD/F and GTR, but LR decreased from 34.3% to 12.0% and NTR increased from 9.8% to 32.0%, $P = .034$ (Figure 1).

Muller grading for hypothalamic involvement/lesion on MRI

Overall, pre-operative Muller grade at time of diagnosis was grade 0 in 2.3%, grade I in 28.7%, grade II in 46.0%, and in 23.0% this was unknown. Post-operatively, at last MRI, Muller's grading was scored as: 18.4% grade 0, 23.0% grade I, and 44.8% as grade II, and 13.8% unknown. In total, 62.7% of children had a stable pre- and post-operative (at last follow-up) Muller grading score, 29.9% had a decrease

in Muller grading, and in 4.5%, the grading increased, of whom all had tumor progression/recurrence requiring multiple treatments (Figure 2).

In children with pre-operative Muller grade II versus grade 0/I, the rate of NTR/GTR resection was statistically lower (OR 0.16 95% CI 0.05–0.47). Overweight or obesity at last follow-up in children with pre-operative Muller grade II was not associated with extensiveness of resection (eCD/F or LR vs. NTR or GTR).

There was no difference in prevalence of grade II pre-operative or post-operative (at last follow-up) Muller grading between patients diagnosed before May 2018 or since May 2018 (pre-operative grade II: 64.3% vs. 52.0% or post-operative grade II: 56.0% vs. 44.0%). When extensiveness of resection (corrected for pre-operative Muller grading) was compared between those diagnosed before or since May 2018, no difference was found (NTR or GTR in Muller grade 0/I: 60.0% vs. 83.3%, respectively and NTR or GTR in Muller grade II: 22.2% vs. 38.5%, respectively).

Tumor progression/recurrence.

In total, 53/87 (60.9%) patients had one or more tumor progression or recurrence events, after a median period of 0.90 years [IQR 0.35–1.61] for the first event. The percentage of patients with tumor progression or recurrence decreased with the extensiveness of the intervention: 20/26 (76.9%) children treated with eCD/F as initial treatment developed tumor progression, 20/24 (83.3%) after LR, 8/14 (57.1%) after NTR, and 5/22 (22.7%) after GTR.

After exclusion of children who received GTR ($n = 22$), children who received RT had significantly lower tumor progression rates (OR 0.24 95% CI 0.07–0.81), adjusted for follow-up time. Thirteen patients who had been undergone limited surgery (eg, eCD/F, LR, or NTR), resulting in tumor residue, had no events of tumor progression without any adjuvant RT (median follow-up time 3.24 years [IQR 1.11–6.24]).

BMI SDS

Overall, mean BMI SDS significantly increased from: 0.75 (SD 1.51) (diagnosis) to 1.81 (SD 1.55) (1 year post diagnosis), 2.02 (SD 1.37) (2 years post diagnosis), to 2.02 (SD 1.59) (last follow-up), $P < .001$. The change in BMI SDS in the first year after diagnosis was the greatest; BMI SDS did not statistically increase after 2 years or at last follow-up. Overall, 11.1% of cCP were obese at diagnosis, which increased to 24.7% at follow-up. Specific interventions for HO (eg, dextro-amphetamines or GLP-1 agonist) have been given to 20.7% of the patients during follow-up, of which 4.6% of $n = 87$ within the first 2 years after cCP diagnosis.

Mean Δ BMI SDS at 1 year was 1.12 (SD 1.15) in patients diagnosed before May 2018 compared to 0.81 (SD 1.23) in patients diagnosed since May 2018, $P = .329$ (Figure 3A). Percentage of patients with obesity after 1 year was 33.3% in patients diagnosed before May 2018 versus 12.0% of the patients diagnosed since May 2018 (OR 0.27 95% CI 0.07–1.10, $P = .067$) (Supplementary Table 1) and at 2 years after diagnosis, obesity rates were 28.6% vs. 6.7%, respectively, $P = NS$.

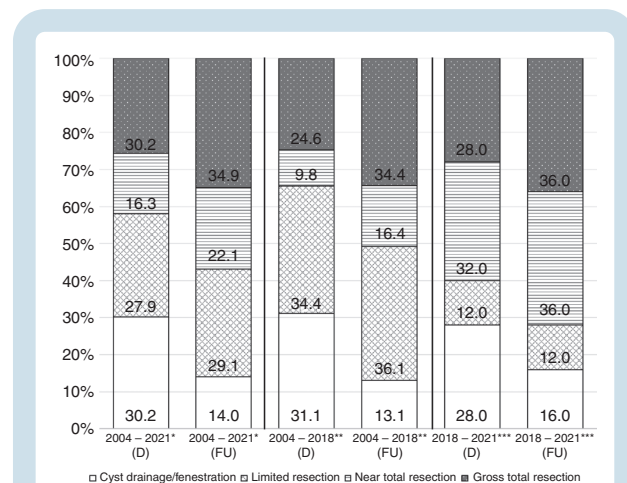


Figure 1. Type of neurosurgical intervention as initial treatment for childhood craniopharyngioma over the years. D: Initial treatment within 3 months of diagnosis, FU: Last follow-up, most invasive resection performed at diagnosis or in case of progression/recurrence throughout follow-up. Type of resection was based on the report of the neurosurgeon in combination with the report of the radiologist, or, if not available, based on the documentation of the treating oncologist. If more than one surgery had been performed in the first 3 months with different types of resection, the most invasive type of resection was chosen.

* Total national cohort, ** Diverse hospitals, *** National center

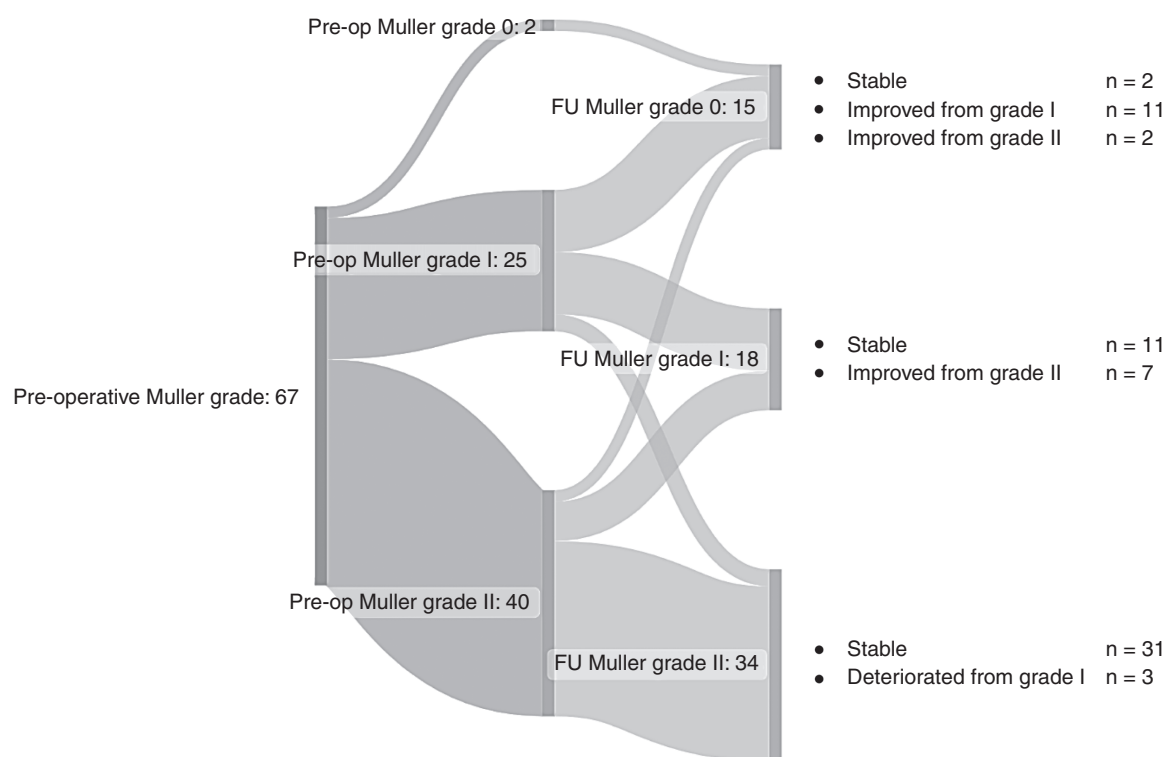


Figure 2. Sankey plot of Muller grading pre-operative and at last follow-up of hypothalamic involvement/lesion on magnetic resonance imaging (MRI) in childhood craniopharyngioma. Muller grading: Grade 0: No hypothalamic involvement/lesion, grade I: Hypothalamic involvement/lesion of the anterior hypothalamus not involving the hypothalamic area beyond mammillary bodies, grade II: Hypothalamic involvement/lesion of the anterior and/or solely posterior hypothalamic area, ie, involving the area beyond mammillary bodies.¹¹ Pre-op: Pre-operative Muller grading (at diagnosis), FU: Follow-up, scoring was based on last available MRI.

Overall, mean BMI SDS at last follow-up was positively associated with higher post-operative Muller grade (at last follow-up): Muller grade 0: BMI SDS 0.81 (SD 0.72) ($n = 16$), Muller grade 1: 1.40 (SD 0.85) ($n = 20$), and Muller grade II: 2.42 (SD 1.98) ($n = 39$), $P = .001$ (Figure 3B). Muller grade II both pre-operatively as well as at last follow-up was associated with presence of overweight or obesity at follow-up (pre-op: OR 8.17 95% CI 2.63–25.32, last follow-up: OR 6.62 95% CI 2.41–18.16). In children whose Muller grade improved (decreased) post-surgically, mean BMI SDS was 1.12 (0.86), which was significantly better than in those whose Muller grading remained stable: mean BMI SDS 2.19 (SD 1.60) $P = .001$, independent of extensiveness of resection.

Extensiveness of resection (eCD/F or LR vs. NTR or GTR) did not significantly influence mean BMI SDS at 1 year, 2 years, or at last follow-up (Figure 3C). Multivariate logistic regression analysis identified BMI SDS at diagnosis and Muller grade II at last MRI of follow-up to be significantly associated with the presence of overweight or obesity at last follow-up (Table 2).

Of the patients with less than GTR ($n = 63$), 52 (82.5%) received growth hormone replacement and 11 patients (17.5%) did not. There was no difference in obesity rates between these 2 groups: 25.0% versus 18.2%, or mean BMI SDS (1.97 vs. 2.10) ($P = \text{NS}$).

Hypothalamic dysfunction.

In 43.7% severe HD (also referred to as having hypothalamic syndrome, a score based on different domains of hypothalamic dysfunction (hyperphagia, hypophagia, BMI, behavioral problems, sleep disorders, temperature regulation disorders, pituitary dysfunction, and radiological Muller grading) was present. Among the children with hypothalamic syndrome, 72.5% had Muller grade II at diagnosis and 79.5% had Muller grade II at last MRI of follow-up. Presence of hypothalamic syndrome at last follow-up, compared between patients diagnosed before May 2018 to those diagnosed since May 2018, (50.8% versus 32.0%) was not statistically different. Presence of hypothalamic syndrome at last follow-up was also not associated with degree of resection (NTR or GTR vs. eCD/F or LR: OR 1.43 95% CI 0.59–3.47).

Pituitary dysfunction at follow-up.

Of all 87 patients, 90.8% had one or more pituitary deficiencies at follow-up. Percentage of patients with panhypopituitarism including DI increased from 5.3% at diagnosis to 71.3% at follow-up. Prevalence of DI increased from 6.6% at diagnosis to 73.6% at last follow-up, of which 6.3% had adipisia at last follow-up. DI at last follow-up was associated with NTR or GTR as initial treatment (OR 6.53

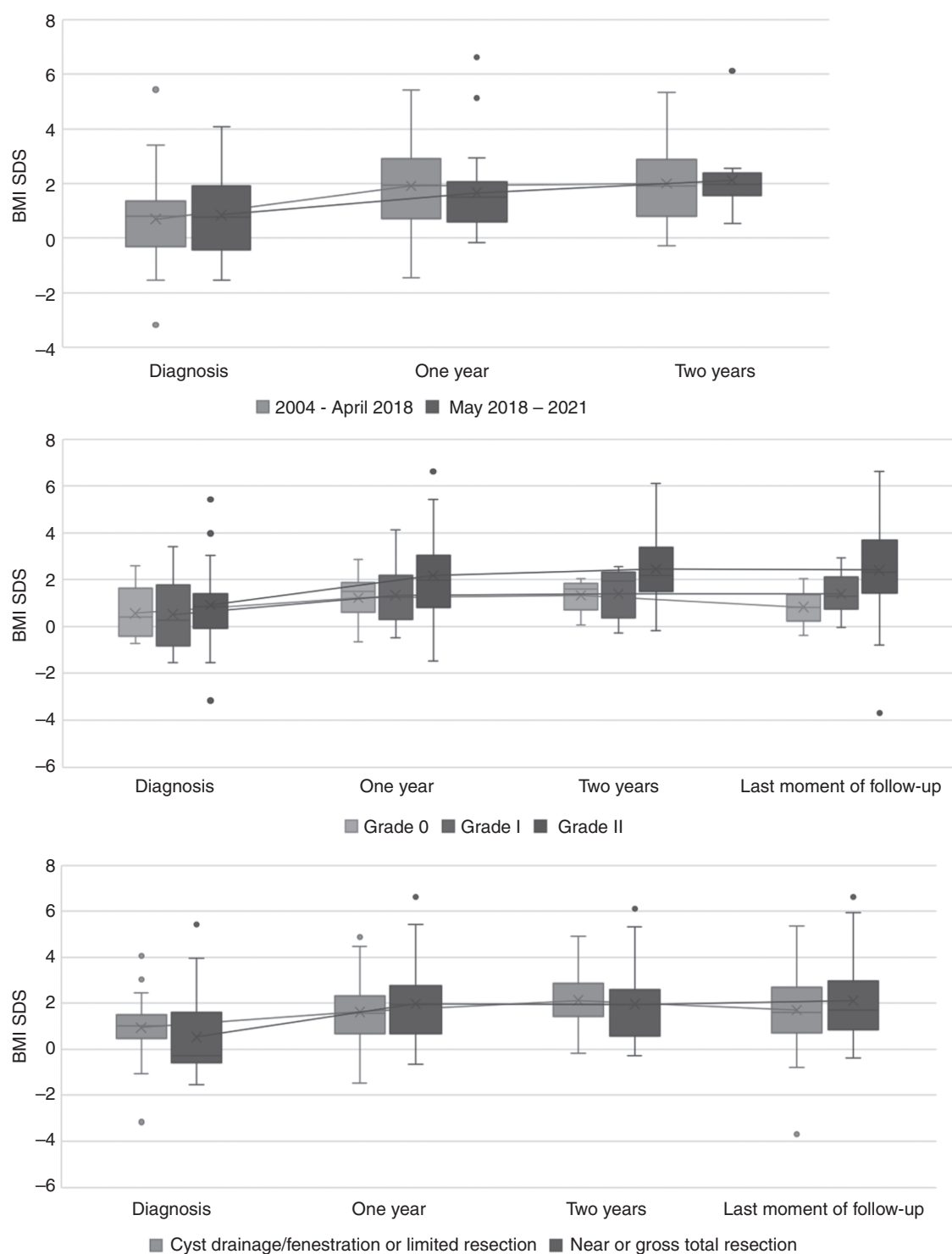


Figure 3. Body mass index (BMI) SDS in childhood craniopharyngioma in time. (A) BMI SDS in childhood craniopharyngioma in relation to year of diagnosis. (B) BMI SDS in relation to Muller grading Muller grading: Grade 0: No hypothalamic involvement/lesion, grade I: Hypothalamic involvement/lesion of the anterior hypothalamus not involving the hypothalamic area beyond mammillary bodies, grade II: Hypothalamic involvement/lesion of the anterior and/or solely posterior hypothalamic area, ie, involving the area beyond mammillary bodies.¹¹ (C) BMI SDS in relation to extensiveness of resection at last follow-up.

Table 2. Risk Factors for Overweight or Obesity at Last Moment of Follow-up in Childhood Craniopharyngioma

	Univariate Analysis				Multivariate Analysis			
	Odds ratio	95% Confidence Interval		P-value	Odds ratio	95% Confidence Interval		P-value
		Lower	Upper			Lower	Upper	
Muller grade II on pre-op MRI ^a	8.17	2.63	- 25.32	<.001*				
BMI SDS at diagnosis	1.67	1.10	- 2.53	.015*	1.78	1.10	- 2.90	.020*
Follow-up time	1.09	0.98	- 1.21	.115	1.05	0.90	- 1.24	.534
GTR or NTR	1.26	0.53	- 3.01	.604	1.34	0.39	- 4.65	.645
Progression or recurrence of the tumor	4.50	1.77	- 11.44	.002*				
Radiotherapy	1.95	0.81	- 4.67	.135				
Clinical HS ^b	9.15	3.28	- 25.54	<.001*				
Muller grade II at last moment of FU ^a	6.62	2.41	- 18.16	<.001*	7.00	1.98	- 24.76	.030*
MB damage (mild or severe) ^c	3.60	1.38	- 9.41	.009*				
Panhypopit at FU	1.91	0.74	- 4.91	.179				
Visual acuity impairments ^d	1.50	0.39	- 5.83	.558				
Visual field impairments ^e	1.23	0.43	- 3.54	.704				

Univariate and multivariable linear regression for risk factors for overweight or obesity compared to normal weight children at last moment of follow-up.

FU, follow-up; GTR, gross total resection; NTR, near total resection; HS, hypothalamic syndrome.

^aPosterior hypothalamic damage graded with Muller: Hypothalamic involvement/lesion of the anterior and/or solely posterior hypothalamic area, ie, involving the area beyond mammillary bodies.¹¹

^bPresence of the hypothalamic syndrome defined by van Santen et al. 2022.²⁵

^cSevere mammillary body damage: severe involvement or damage (unrecognizable structures or both sided damaged) of the mammillary bodies.

^dModerate, severe or blindness of both eyes (best-corrected visual acuity of >0.5 logMAR for both eyes).

^eVisual field impairments: only types of hemianopsia (homonymous, heteronymous, or quadrantic) was classified as present (reported by the ophthalmologist).

*statistically significant.

95%CI 1.76 - 24.23). There was no difference in prevalence of DI between patients with or without radiotherapy (76.6% vs. 72.5%).

There was no difference in one or more pituitary deficiencies (90.3% vs. 92.0%), DI (69.4% vs. 72.0%), or panhypopituitarism with DI (72.6% vs. 68.0%) between patients diagnosed before or since May 2018. In total 9.2% had a normal pituitary function after a mean follow-up period of 5.62 years (SD 3.25).

Visual function at follow-up.

In 22.0% of cCP, visual acuity improved and in 14.6% visual acuity decreased. In 11.9% visual field impairments improved and in 33.3% visual field deficits (of which 42.9% hemianopsia) remained present at last follow-up. In 33.3% (of which 50.0% hemianopsia) visual field impairments were newly developed after treatment. The percentage of patients with moderate or severe loss of visual acuity or blindness of both eyes (12.8% vs. 14.8%) and visual field impairments at last follow-up (55.3% vs. 60.0%) remained similar among those diagnosed before or since May 2018. **Figure 4** displays all differences in outcomes of cCP before and after centralization of care.

Discussion

We aimed to evaluate trends in given treatment and hypothalamic outcomes in a Dutch cohort of cCP diagnosed between 2004 and 2021 and to study the possible effect of centralization of care. Within this national cohort, in line with literature,^{11,15-18,29-32} the frequency of GTR was performed in a relatively low percentage of the patients (only 25.4% of all patients). In addition, GTR appeared not to be associated with HO. After centralization of care a trend towards lower obesity rates in the first 2 years after diagnosis was observed. Lastly, we found that the increase in BMI SDS was most significant in the first year following surgery with no statistical further increase in the years thereafter.

In the Netherlands, a unique situation has emerged since May 2018 when care and follow-up for cCP patients have been largely centralized. When comparing groups by date of diagnosis (those diagnosed before May 2018 and those since), we found that the rates for GTR and eCD/F remained unchanged, but the rates for NTR increased and LR decreased. However, when adjusting for Muller grading, percentages of extensiveness of resection were

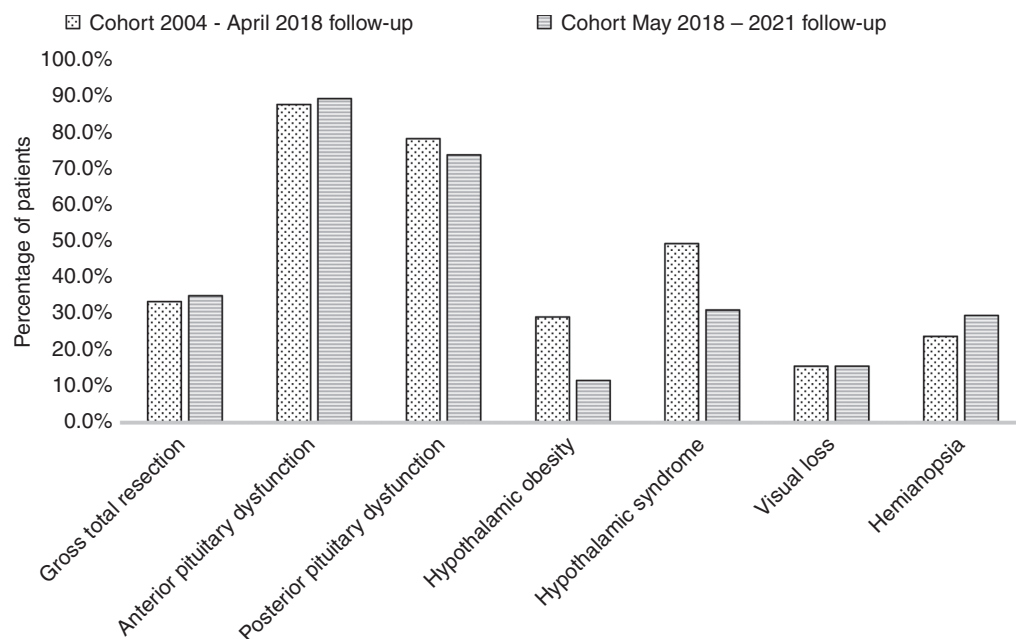


Figure 4. Differences in outcomes of cCP before and after centralization of care. Gross total resection was defined as having removed all tumor tissue, stated both by the neurosurgeon and radiologist. Anterior pituitary deficiency was defined as one or more anterior pituitary deficiencies, eg, growth hormone deficiency, thyroid-stimulating hormone deficiency, adrenocorticotrophic hormone deficiency, or gonadotrophin deficiency. Posterior pituitary dysfunction was defined as central diabetes insipidus and/or central precocious puberty. Hypothalamic syndrome was present based on the diagnostic criteria of van Santen et al.²⁵ Visual loss was defined as moderate or severe loss of visual acuity or blindness of both eyes (>0.5 logMAR).

not significantly different between the 2 groups. Possibly surgical strategy has been more carefully selected as a result of the centralized, multidisciplinary environment, which allowed for a more extensive operative approach to be pursued in the appropriate population of patients. The option to choose the optimal type of resection, either endoscopic transsphenoidal resection in case of sellar craniopharyngiomas or transcranial microscopic resection in large suprasellar craniopharyngiomas have been available in all treating centers both before 2018 and post-2018, after centralization.

Interestingly, “despite” this shift toward more extensive resection, we found a lower Δ BMI SDS in the first year after diagnosis and lower rates of obesity in the first and second year after diagnosis. Rates of pituitary dysfunction, visual loss, or hemianopsia did not change between the 2 cohorts (Figure 4), so research on improvement in outcome in these domains is still much needed. The small sample size warrants careful interpretation and may have affected statistical significance of these findings. Future studies with longer follow-up times and larger sample sizes are definitely needed to put these results in perspective.

In the diagnostic phase of a patient suspected of childhood cCP, detailed diagnostic imaging, preferably using MRI, should be used to define anatomical characteristics of the hypothalamic lesion resulting from the tumor. Grading hypothalamic involvement by MRI with a previously developed scoring system (eg, Muller grade), can help to define the estimate the severity of hypothalamic damage. The advantage of the Muller grade is that this scoring system takes pre-operative involvement and post-operative

lesions into account. Muller grading has previously been described to be related to HD.¹¹

In our cohort, a less extensive resection aiming to avoid additional hypothalamic damage was indeed performed in patients with grade II pre-operative Muller grading on MRI (use of NTR or GTR in Muller grade II OR 0.16 95% CI 0.05–0.47). Interestingly, in those who improved according to Muller grading, BMI was significantly better at follow-up, but this was independent of extensiveness of resection. This may imply, that in these children the hypothalamus was displaced but not damaged and that extensive resection in such children can be reached without hampering hypothalamic function after carefully considering the vulnerability of this structure. It also illustrates that anatomical and functional outcomes are different aspects that should be evaluated separately.²⁸ Unfortunately, we did not perform extensive hypothalamic functional scoring pre-operatively in this cohort, and with the retrospective data, this could only partially be accomplished post-operatively. For future cohorts, we advise that detailed pre-operative hypothalamic screening is done, using the clinical hypothalamus function score²⁷ and radiological assessment to better understand which patients are at risk to develop further hypothalamic damage. It must be acknowledged that the Muller grading for hypothalamic damage is still quite robust, and therefore future research should focus on improving radiological techniques to provide more detailed information on the anatomical relationship of the tumor to the different nuclei of the hypothalamus (e.g. arcuate nucleus, paraventricular nucleus, and dorsomedial nucleus), which will not only help the surgeon to define its margins,

but will also enable more appropriate counseling of the patient with regards to what may be expected following surgery. In addition, it appears relevant for future research to realize that the neurosurgical resection will also be determined by the tumor tissue characteristics like consistency and micro-invasiveness into the environment affecting the options to mobilize the tumor by gentle traction. Therefore, a pre-operative intention to treat and a post-operative detailed evaluation of operative treatment by the neurosurgeon could be valuable to address the surgical outcome. This aspect requires a prospective study design.

In our cohort, we found high percentages of patients with panhypopituitarism and DI, when compared to literature.^{14,30–33} DI is in general considered to be an adverse event of surgery, and is never seen as late effect after RT.³⁴ This was consistent with the results in our cohort, as more aggressive surgery (NTR or GTR) was associated to the presence of DI, while there was no difference in presence of DI in patients with or without radiotherapy. Future cohorts should take initial surgical intent into account, as this may also have influenced the high percentage of DI in our cohort.

RT is considered one of the pillars in cCP treatment and might be expected to increase in use when LR is aimed for. In our cohort, 13 patients with tumor residue after initial treatment had no events of tumor progression or recurrence without any adjuvant RT (median follow-up time 3.24 years [IQR 1.11–6.24]). This may plead for a wait-and-scan policy after LR; however, longer follow-up time is needed to confirm this. Delayed RT until disease progression can be beneficial and even crucial in young children where the intended effect of tumor control must be balanced against its possible adverse effects, such as additional hypothalamic-pituitary damage, cognitive decline, and vascular injuries.^{29,35} In future studies, it will be of interest to compare progression/recurrence rates, hypothalamic-pituitary outcome, and adverse effects of surgery and RT in larger international cohorts.

HO has been described to occur in 17%–74% of cCP patients.^{14,31–33} In the Netherlands, 2 previous cCP cohorts ($n = 84$) were described, diagnosed between 1980 and 2015, with obesity rates between 64.0% and 74.0%.^{32,33} In our current cohort, obesity rates at follow-up seem to be lower (24.7%) compared to the other 2 Dutch cohorts previously reported. From May 2018 onwards, we have had a unique situation in the Netherlands, as care and follow-up for cCP has been largely centralized in the national pediatric neuro-oncological expert center including a unique multidisciplinary hypothalamic expert team, also including endocrinology, rehabilitation, dietary, psychology, and physiotherapy expertise. Obesity rates 1 and 2-year post-diagnosis in cohort of May 2018–2021 further decreased to 12.0% and 6.7%, respectively, which may point towards positive effect of centralization of care and increase in expertise of the multidisciplinary team. Specific interventions for HO (eg, dextro-amphetamines or GLP-1 agonists) have been given to 20.7% of the cCP in this cohort, which did not differ between patients diagnosed before May 2018 versus patients diagnosed since May 2018. Future studies will have to further explore the factors that contribute to this improvement in BMI outcomes.

In the multivariate analysis, comparable to previous studies, BMI SDS at diagnosis was significantly associated

with overweight or obesity at follow-up.⁹ The fact that hypothalamic damage is already present at time of diagnosis implies perhaps that limiting the extent of neurosurgical resection may not be able to reverse this damage, and BMI at diagnosis may therefore be more predictive of hypothalamic outcome than Muller grading at diagnosis. In addition, the fact that BMI SDS increases most significantly in the first year after diagnosis, emphasized the importance of starting interventions for obesity as soon as possible. We recommend monitoring BMI changes closely following surgery and to start interventions more quickly to prevent occurrence or aggravation of obesity.^{33,36} In addition, it is relevant to create awareness for the consequences of neglecting BMI change in the first weeks following surgery, as this may quickly develop into obesity. Multidisciplinary support must be offered to patients and parents from the moment of diagnosis, focusing on limiting the consequences of hypothalamic damage with lifelong lifestyle adjustments with medical and psychosocial support. Future research should focus on unraveling the factors that contribute to this extreme weight gain in the first year enabling the development of new ways for prevention and treatment of HO.

Several limitations of our study should be considered, such as the retrospective study design, the lack of a control group, and missing data of patients with longer follow-up time. Due to the fact that the data for this study were collected retrospectively from 8 different university hospitals and since May 2018 from the Princess Máxima Center, there was variability in availability of data. Also, it may be outweighed that our cohort possibly reflects the patients with the worse hypothalamic outcome as they attend our specialized follow-up clinic.

In conclusion, in this large Dutch cohort of 87 cCP patients diagnosed in the period 2004–2021 with long follow-up time (maximum of 16 years), we found BMI SDS at diagnosis to be the most important risk factor for overweight/obesity at follow-up, but no association with extent of neurosurgery (after careful selection of patients using pre-operative radiological assessment of hypothalamic involvement). Centralization of care seems to be beneficial for BMI outcome, although this result must be followed in time. With increase of BMI mostly significantly in the first year post-surgery, we advocate to start interventions for HO in the first year after diagnosis. Future collaborative research with larger international cohorts may help to define the optimal treatment strategy for cCP with the aim to limit hypothalamic damage.

Supplementary material

Supplementary material is available online at *Neuro-Oncology* (<http://neuro-oncology.oxfordjournals.org/>).

Keywords

Craniopharyngioma | hypothalamic obesity | muller grade | surgical treatment

Funding

No funding was secured for this study.

Acknowledgments

We want to thank Prof. E van den Akker and Dr. T Sas for their support in data collection.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Author Contributions

Drs. J van Schaik conceptualized and designed the study, contributed to the acquisition, analysis and interpretation of the data, drafted the initial manuscript, and reviewed and revised the manuscript. Dr. AYN Schouten-van Meeteren, Dr. E de Vos-Kerkhof, Dr. GO Janssens, Prof. GL Porro, Dr. B Bakker, Prof. M Fiocco, Prof. WJE Tissing contributed to the analysis and interpretation of the data and reviewed and revised the manuscript. Prof. Eelco Hoving and Dr. Hanneke van Santen conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Given the retrospective character of the data-analysis, the local institutional review board (METC Utrecht, the Netherlands) decided that the Act on Medical Research Involving Human Subjects did not apply and provided a waiver (20-640/C). Written informed consent was obtained for participation in this study.

Informed Consent

Written informed consent was obtained from the participants' parent/legal guardian/next of kin and/or patient itself (if age 12 and up) to participate in the study.

Data Availability

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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References

1. Habibi, Z., D.A. Reesh, and J.T. Rutka, *Craniopharyngioma: Current Classification, Management, and Future Directions, in Oncology of CNS Tumors*, J.-C. Tonn, et al., eds. Cham: Springer International Publishing; 2019. p. 561–583.
2. Nuijts M, Veldhuis N, Stegeman I, et al. Visual function in children with craniopharyngioma at diagnosis: A systematic review. *Neuro Oncol*. 2020;22(suppl_3):iii455–iii456.
3. Muller HL. Childhood craniopharyngioma--current concepts in diagnosis, therapy and follow-up. *Nat Rev Endocrinol*. 2010;6(11):609–618.
4. Muller HL, Merchant TE, Warmuth-Metz M, Martinez-Barbera J-P, Puget S. Craniopharyngioma. *Nat Rev Dis Primers*. 2019;5(1):75.
5. Dimitri P. Treatment of acquired hypothalamic obesity: Now and the future. *Front Endocrinol (Lausanne)*. 2022;13:846880. doi: [10.3389/fendo.2022.846880](https://doi.org/10.3389/fendo.2022.846880). PMID: 35464063; PMCID: PMC9019363.
6. Zada G, Kintz N, Pulido M, Amezcua L. Prevalence of neurobehavioral, social, and emotional dysfunction in patients treated for childhood craniopharyngioma: A systematic literature review. *PLoS One*. 2013;8(11):e76562.
7. van Iersel L, Brokke KE, Adan RAH, et al. Pathophysiology and individualized treatment of hypothalamic obesity following craniopharyngioma and other suprasellar tumors: A systematic review. *Endocr Rev*. 2019;40(1):193–235.

8. Bogusz A, Boekhoff S, Warmuth-Metz M, et al. Posterior hypothalamus-sparing surgery improves outcome after childhood craniopharyngioma. *Endocr Connect*. 2019;8(5):481–492.
9. van Iersel L, Meijneke RWH, Schouten-van Meeteren AYN, et al. The development of hypothalamic obesity in craniopharyngioma patients: A risk factor analysis in a well-defined cohort. *Pediatr Blood Cancer*. 2018;65(5):e26911.
10. Muller HL, Gebhardt U, Faldum A, et al; Kraniopharyngeom 2000 Study Committee. Xanthogranuloma, Rathke's cyst, and childhood craniopharyngioma: Results of prospective multinational studies of children and adolescents with rare sellar malformations. *J Clin Endocrinol Metab*. 2012;97(11):3935–3943.
11. Muller HL, Gebhardt U, Teske C, et al; Study Committee of KRANIOPHARYNGEOM 2000. 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*. 2011;165(1):17–24.
12. Sanford RA. Craniopharyngioma: Results of survey of the American Society of Pediatric Neurosurgery. *Pediatr Neurosurg*. 1994;21(suppl 1):39–43.
13. Thompson D, Phipps K, Hayward R. Craniopharyngioma in childhood: Our evidence-based approach to management. *Childs Nerv Syst*. 2005;21(8-9):660–668.
14. Puget S, Garnett M, Wray A, et al. Pediatric craniopharyngiomas: Classification and treatment according to the degree of hypothalamic involvement. *J Neurosurg*. 2007;106(1 suppl):3–12.
15. Hill TK, Baine MJ, Verma V, et al. Patterns of care in pediatric craniopharyngioma: Outcomes following definitive radiotherapy. *Anticancer Res*. 2019;39(2):803–807.
16. Muller HL, Gebhardt U, Pohl F, et al. Relapse pattern after complete resection and early progression after incomplete resection of childhood craniopharyngioma. *Klin Padiatr*. 2006;218(6):315–320.
17. Rao YJ, Hassanzadeh C, Fischer-Valuck B, et al. Patterns of care and treatment outcomes of patients with Craniopharyngioma in the national cancer database. *J Neurooncol*. 2017;132(1):109–117.
18. Schoenfeld A, Pekmezci M, Barnes MJ, et al. The superiority of conservative resection and adjuvant radiation for craniopharyngiomas. *J Neurooncol*. 2012;108(1):133–139.
19. DeNunzio NJ, Yock TI. Modern radiotherapy for pediatric brain tumors. *Cancers (Basel)*. 2020;12(6):1533. PMID: 32545204; PMCID: PMC7352417.
20. Henderson F, Jr., Schwartz TH. Update on management of craniopharyngiomas. *J Neurooncol*. 2022;156(1):97–108.
21. Muller HL. The diagnosis and treatment of craniopharyngioma. *Neuroendocrinology*. 2020;110(9–10):753–766.
22. Casparie M, Tiebosch ATMG, Burger G, et al. Pathology databanking and biobanking in The Netherlands, a central role for PALGA, the nationwide histopathology and cytopathology data network and archive. *Cell Oncol*. 2007;29(1):19–24.
23. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: International survey. *BMJ*. 2000;320(7244):1240–1243.
24. Cole TJ, Flegal KM, Nicholls D, Jackson AA. Body mass index cut offs to define thinness in children and adolescents: International survey. *BMJ*. 2007;335(7612):194.
25. Moussa G, Bassilious K, Mathews N. A novel excel sheet conversion tool from Snellen fraction to LogMAR including “counting fingers,” “hand movement,” “light perception” and “no light perception” and focused review of literature of low visual acuity reference values. *Acta Ophthalmologica*. 2021;99(6):E963–E965.
26. Nuijts MA, Stegeman I, van Seeters T, et al. Ophthalmological findings in youths with a newly diagnosed brain tumor. *JAMA Ophthalmol*. 2022;140(10):982–993.
27. van Santen HM, van Schaik J, van Roessel IMAA, et al. Diagnostic criteria for the hypothalamic syndrome in childhood. *Eur J Endocrinol*. 2023;188(2):lvad009. PMID: 36737045.
28. Van Schaik J, et al. Resting energy expenditure in children at risk of hypothalamic dysfunction. *Endocr Connect*. 2022;11(8):e220276. PMID: 35904233; PMCID: PMC9346331.
29. Erfurth EM. Diagnosis, background, and treatment of hypothalamic damage in craniopharyngioma. *Neuroendocrinology*. 2020;110(9–10):767–779.
30. Marcus HJ, Rasul FT, Hussein Z, et al. Craniopharyngioma in children: Trends from a third consecutive single-center cohort study. *J Neurosurg Pediatr*. 2019:1–9.
31. Tosta-Hernandez PDC, Siviero-Miachon AA, da Silva NS, et al. Childhood craniopharyngioma: A 22-year challenging follow-up in a single center. *Horm Metab Res*. 2018;50(9):675–682.
32. Wijnen M, van den Heuvel-Eibrink MM, Janssen JAMJL, et al. Very long-term sequelae of craniopharyngioma. *Eur J Endocrinol*. 2017;176(6):755–767.
33. van Iersel L, Meijneke RWH, Schouten-van Meeteren AYN, et al. The development of hypothalamic obesity in craniopharyngioma patients: A risk factor analysis in a well-defined cohort. *Pediatric Blood & Cancer*. 2018;65(5):e26911.
34. van Iersel L, Mulder RL, Denzer C, et al. Hypothalamic-pituitary and other endocrine surveillance among childhood cancer survivors. *Endocr Rev*. 2022;43(5):794–823.
35. Aggarwal A, Fersht N, Brada M. Radiotherapy for craniopharyngioma. *Pituitary*. 2013;16(1):26–33.
36. van Schaik J, Welling MS, de Groot CJ, et al. Dextroamphetamine treatment in children with hypothalamic obesity. *Front Endocrinol (Lausanne)*. 2022;13:845937.