Posterior Hypothalamus-sparing Surgery improves Outcome after Childhood Craniopharyngioma

Running title: Surgical strategies in craniopharyngioma

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Abstract

**Objective:** Quality of life (QoL) is frequently impaired in childhood-onset craniopharyngioma (CP) by hypothalamic syndrome. The debate, whether pretreatment hypothalamic involvement (HI) has apriori prognostic impact or surgical hypothalamic lesions (HL) determine outcome, is controversial.

**Design:** Survival and outcome of CPs recruited 2007–2014 in KRANIOPHARYNGEOM 2007 were analyzed with regard to reference-confirmed presurgical HI and surgical HL. **Methods:** Radiological findings, body mass index (BMI) and QoL were assessed at diagnosis, and during follow-up. QoL was assessed using Pediatric Quality of Life (PEDQOL) questionnaire. **Results:** 169 CP were included presenting with no HI (n=11), anterior (n=49), and anterior+posterior (a+p) HI (n=109) prior to surgery. The latter 109 were analyzed for post-operative HL (no lesion: n=23, anterior HL: n=29, a+pHL: n=57). Progression-free survival (PFS) was higher after complete resection. The highest PFS was observed in CP with a+pHL, especially when compared between non-irradiated subgroups \( p=0.006 \). Overall survival (OS) rates were 1.0 in all subgroups. CP with a+pHL developed higher BMI \( (p \leq 0.001) \) during follow-up compared between subgroups. 55/109 pts with a+pHI completed PEDQOL at diagnosis (48/109 at 3 years follow-up). QoL was worse for a+pHL patients in terms of physical, social and emotional functionality when compared with the anterior HL and no HL subgroup. BMI development and QoL during follow-up were similar for patients with anterior HL and without HL. **Conclusions:** Posterior hypothalamus-sparing surgical strategies are associated with higher QoL, decreased development of obesity, and lower PFS in CP.

**Keywords:** Craniopharyngioma; hypothalamus; obesity; quality of life; surgery.
Introduction

CPs are rare, histologically benign (WHO I°), embryonal malformations of the sellar/parasellar area originating from neoplastic transformation of ectodermal-derived epithelial cell remnants of Rathke’s pouch and the craniopharyngeal duct (1-6). Overall survival rates after CP are high (87 to 95% 20-years overall survival) (7). However, in long-term survivors quality of life (QoL) is frequently reduced due to morbidity caused by close anatomical proximity of CP to hypothalamic–pituitary axes (8-10). Improvements of prognosis in terms of QoL and PFS will only be achieved by multidisciplinary, risk-adapted neurosurgical and radiooncological treatment strategies, which provide appropriate medical and psychosocial support for CP patients (11-13).

Disease-related and/or surgical hypothalamic lesions (HL) are associated with clinical significant impairments of overall survival and long-term QoL. However, the debate whether primary hypothalamic involvement (HI) has major and apriori impact on prognosis and outcome or whether treatment-related, surgical HL is the determining risk factor for sequelae is controversial.

Accordingly, we prospectively analyzed a large cohort of CP patients with initial preoperative involvement of anterior and posterior (a+p) hypothalamic structures for postoperative QoL, body mass index (BMI) and functional capacity with regard to reference-confirmed degree of surgical hypothalamic damage.

Patients and methods

Patients

178 (94 females / 84 males) diagnosed with adamantinomatous CP (median age at diagnosis: 9.3 years, range: 1.3–17.9 years) were recruited between 2007 and 2014 in our multinational trial KRANIOPHARYNGEOM 2007 (NTC00258453) (14) and observed prospectively during follow-up of at least 3 years.

The degree of initial presurgical HI could be reference-assessed in 169 of 178 (95%) patients. 11 of these 169 CP patients (6%) presented without HI at time of diagnosis, 49 (29%) were initially diagnosed with HI of anterior hypothalamic structures, and 109 (64%) were primarily diagnosed with preoperative HI of a+p hypothalamic areas. We analyzed survival rates in all patients. Furthermore,
BMI SDS in these 109 patients with presurgical, a+pHI was analyzed at the time of diagnosis, at one and 3 years after CP diagnosis and at last follow-up visit. QoL could be analyzed by the Pediatric Quality of Life (PEDQOL) questionnaire at diagnosis in 55 of these 109 CP patients (50%) and during follow-up in 48 of 109 patients at standardized time points. Low patient number (55 of 109) is due to the following limitations 1.) missing data on QoL assessment at the time point 3 years after CP diagnosis in 30 patients, 2.) incomplete QoL assessment (e.g. parental assessment was not completed) in 13 CP patients, and 3.) missing data on QoL in 11 patients.

Clinical parameters

Auxiological and clinical parameters were collected in all patients based on the KRANIOPHARYNGEOM 2007 trial protocol. Body height (SDS) (15) and body weight were obtained at diagnosis and prospectively at 3-months intervals after CP diagnosis. BMI (w/h2; w= weight/kilogram, h= height/meter) was calculated and depicted as SDS according to the references of Rolland-Cachera et al. (16) for each subject at CP diagnosis and at standardized time points (one and 3 years after CP diagnosis, and at last follow-up visit).

Neuroimaging

Cranial MRIs were performed according to the KRANIOPHARYNGEOM 2007 protocol (17-19) at the time of CP diagnosis and prospectively at 3-months intervals during follow-up. Neuroradiological assessment of CP location, degree of surgical resection, preoperative HI and surgical HL was performed on pre- and postoperative axial, coronal and sagittal MRIs by a reference neuroradiologist (M.W.-M.) blinded for clinical and surgical information. CP location was categorized according to the degree of HI: no HI detectable on presurgical MRIs; HI of anterior hypothalamic structures not involving mammillary bodies and hypothalamic structures dorsal of mammillary bodies; and HI of both a+p hypothalamic areas, i.e. involving anterior hypothalamic structures, mammillary bodies and hypothalamic areas dorsal of mammillary bodies (17, 18). Surgical HLs were graded based on postsurgical MRIs according to the same criteria in 3 categories: none HL: no HL detectable on postsurgical MRIs, anterior HL: HL of anterior hypothalamic structures not involving mammillary
bodies, and a+PHL: HL involving anterior hypothalamic structures, mammillary bodies and hypothalamic areas dorsal of mammillary bodies (Figure 1).

Treatment
Neurosurgical treatment data were analyzed with regard to surgical approach, degree of surgical resection, and center size of neurosurgical institutions based on patient load during 7 years of CP recruitment in KRANIOPHARYNGEOM 2007 (small-sized centers: one patient; middle-sized centers: 2-5 patients; large-sized centers: >5 patients per 7 years recruitment period in KRANIOPHARYNGEOM 2007). Radiooncological treatment data were analyzed for radiation technique, age at initiation, and radiation dose. In KRANIOPHARYNGEOM 2007, the decision on time point of irradiation (immediate irradiation vs. irradiation at the time point of progression of residual tumor) was randomized for a small subgroup of patients (n=24) fulfilling the following inclusion criteria for the randomized trial: a. 5 years or older at diagnosis and b. reference-confirmed incomplete resection. In all the other patients recruited in KRANIOPHARYNGEOM 2007, the decision on radiotherapy was made by the local treating teams at participating hospitals according to the study recommendation to perform irradiation after incomplete resection. Endocrine status was assessed with regard to hormonal substitution of deficient hypothalamic–pituitary axes.

Quality of life questionnaires
In CP patients diagnosed at an age ≥5 years, the Pediatric Quality of Life (PEDQOL) (20) questionnaire was used to analyze QoL at standardized time points (one and 3 years after CP diagnosis). Additionally, parental assessment of patient QoL was obtained by PEDQOL in patients younger than 18 years at study. The PEDQOL questionnaire is defining health-related QoL within seven domains (autonomy, emotional functionality, body image, cognition, physical function, social functionality in family, and social functionality among friends). A high score is equivalent to more negative self or parental QoL assessment (20).
The German daily life ability scale Fertigkeitsenkala Münster-Heidelberg (FMH) was used to analyze functional capacity as a measure of QoL at the standardized time points 3 months, one and 3 years after CP diagnosis and at last visit. FMH assesses the capacity for routine actions in daily life with 56 items. It was normalized with 971 persons (45% female), aged between 0 and 102 years, resulting in age-dependent percentiles (21). The average time for answering the FMH questionnaire is 4.5 minutes in first-time users (22).

**Statistical methods**

Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA). Mann–Whitney U test or Kruskal-Wallis test were used for comparison of continuous variables between two or more independent groups and Wilcoxon Signed-Rank test or Friedmann test were used for comparison of two or more related groups for continuous variables. Fisher test was used for comparison of different groups for categorical variables. Progression-free survival (PFS) and overall survival (OS) rates were estimated by Kaplan–Meier analyses and groups were compared using the log-rank test. Events for estimation of PFS were defined as neuroradiologically confirmed >20% progression of residual tumor, reference-confirmed tumor recurrence after reference-confirmed complete surgical resection, and death. The local significance level is set to 0.05, i.e. p-values of ≤0.05 were considered statistically noticeable. No adjustment for multiple testing was applied. Therefore, inferential statistics are intended to be exploratory (hypotheses generating), not confirmatory, and are interpreted accordingly.

**Results**

One-hundred seventy-eight (94 females / 84 males) patients diagnosed with CP (median age at CP diagnosis: 9.3 years, range: 1.3 – 17.9 years) were recruited between 2007 and 2014 in our multinational, prospective KRANIOPHARYNGEOM 2007 trial (NTC00258453) (14). The histological diagnosis of adamantinomatous CP was confirmed by neuropathological reference assessment in all cases. Neurosurgical interventions were performed at 63 German, Austrian or Swiss neurosurgical institutions. Case distribution with regard to HI and HL over neurosurgical centers of
different center size categorized according to patient load over 7 years recruitment (34 small-sized, 21 middle-sized, and 8 large-sized neurosurgical centers) is depicted in Table 1. The occurrence of surgical posterior HL was similarly distributed with regard to center size (no posterior HL: small-sized centers 62%, middle-sized centers 68%, large-sized centers 67%; posterior HL: small-sized centers 38%, middle-sized centers 32%, large-sized centers 33%).

In 169 of 178 recruited patients (95%), the initial degree of HI and surgical HL could be reference-assessed. 11 of these 169 CP patients (7%) presented without HI at time of diagnosis, 49 (29%) were initially diagnosed with HI of anterior hypothalamic structures, and 109 (64%) were primarily diagnosed with preoperative HI of a+p hypothalamic areas (Table 1). These 109 CP patients diagnosed with preoperative involvement of a+p hypothalamic areas were included in our analysis of survival and weight development during follow-up. In 55 of these 109 CP patients (50%), PEDQOL were available for analysis of QoL. Functional capacity was assessed in all 109 CP patients during follow-up. Surgical HL were reference-confirmed in 86 of 109 (79%) CP patients (Table 2).

Data on degree of surgical resection performed at 63 German, Austrian or Swiss neurosurgical centers were missing in 12 of 109 patients (11%). Complete resection could be achieved in 77 of 97 patients (80%) and incomplete resections in 20 of 97 patients (21%). After complete surgical resection, CP patients showed a higher PFS (p=0.02) when compared with PFS of patients after incomplete resection (Figure 2A). The degree of surgical resection differed noticeably with regard to surgical HL (p<0.0001). As expected per inclusion criteria, complete surgical resections always resulted in a+pHL (20/20). Incomplete resections were performed more frequently in patients without (79%) or anterior HL (97%) than in patients with a+pHL (54%). Overall survival rates (1.0 in all subgroups with different degree of HL) were similar, i.e. no events were observed during follow-up. PFS rates were similar with regard to degree of HL (Figure 2B). However a trend towards higher PFS was observed in the a+pHL cohort, when compared with the subgroups presenting postoperatively without or anterior HL. When adjusted for irradiation by analyzing the subgroup of non-irradiated patients, the PFS rate was noticeably higher in non-irradiated patients with a+pHL (p=0.006) (Figure 2C). Furthermore, the pairwise comparison of the subgroups a+pHL and anterior HL shows a statistically noticeable difference concerning PFS (p=0.03).
Baseline BMI SDS was similar in all HL subgroups at the time of diagnosis. Significant increases in BMI occurred in all HL subgroups during follow-up (median follow-up interval at last visit: 6.1 years, range: 3.01 – 10.21 years). However, CP with a+pHL presented with higher BMI at the time points 1 year after diagnosis (median BMI: +5.21 SD, range: -0.32 – 13.09 SD) and at last visit (median BMI: +5.74 SD, range: -0.82 – 14.65 SD), when compared to patients without HL (median BMI at 1 year follow-up: +1.72 SD, range: 1.54 – 8.09 SD, p=0.001; at last visit: +2.33 SD, range: -1.77 – 10.98 SD, p<0.001) and compared to patients with anterior HL (median BMI at 1 year follow-up: +2.46 SD, range: -1.86 – 10.37 SD, p=0.002; at last visit: +2.87 SD, range: -0.81 – 11.11 SD, p=0.001). The development of severe obesity in patients with a+p HL was due to significant weight increase during the first year after diagnosis (p<0.001). Further significant increases of BMI SDS were not detectable after the first postsurgical year in any of the subgroups with different degree of HL (Figure 3).

QoL in CP patients was parental and self-assessed by PEDQOL questionnaire during follow-up. At the time point one year after CP diagnosis, differences for PEDQOL domains did not reach statistical significance with regard to HL neither for self nor for parental assessment of QoL (Figure 4 A,C). Self-assessed QoL in patients with a+pHL significantly decreased between one and 3 years after surgery for the PEDQOL domains social functionality friends (p=0.050) and family (p= 0.016. Decreased QoL was observed during further follow-up in CP with a+pHL when compared with CP patients without HL. At the time point 3 years after diagnosis, patients without HL scored better for the PEDQOL domain social functionality (family) in self and parental assessment (p=0.014, p=0.002), whereas better scores for the PEDQOL domains physical function (p=0.047), emotional stability (p=0.040) were observed for patients without HL only in parental assessment, when compared to CP patients with a+pHL (Figure 4 B,D). At the time point one year after surgery, parents estimated QoL worse with regard to PEDQOL domains emotional stability, body image and physical functionality than patients in all respective HL subgroups. At the time point 3 years after surgery, parental rating for the PEDQOL domains physical function (p=0.026) and social functionality with friends (p=0.028) was worse for the subgroup of patients with a+pHL (Figure 4). Differences in terms of functional capacity did not reach statistical significance during follow-up with regard to HL (Figure 5).

In 10 patients, it was not clarified if irradiation was performed. 46 of 99 patients (47%) were irradiated.
with conventional fractionated target volume doses of 50.4 – 54.0 Gy (mean dose: 53.3 Gy). One case was treated by Gamma Knife with a volume doses of 24 Gy. 23 of 46 irradiated CP patients (50%) were treated by photon irradiation; 23 of 46 patients (50%) received proton beam therapy. The highest rate of irradiation was observed in the cohort without HL (70%) when compared to the subgroup with anterior HL (52%) and patients with a+pHL (28%) (p=0.004) (Table 2).

Noticeable differences in terms of endocrine deficiencies were not observed between the CP patient subgroups of irradiated and non-irradiated patients with different degree of HL at last visit except for central diabetes insipidus. Diabetes insipidus was observed more frequently in patients with HL, with the difference being statistically noticeable in the subgroup of irradiated patients (p=0.030). However, the analysis of association of HL and endocrine deficiencies is limited due to small sample size and incomplete data (Table 3).

Discussion

Hypothalamic syndrome and the development of morbid obesity are major sequelae with negative impact on prognosis after CP (23). However, there is still considerable debate (24-27), whether initial presurgical HI or treatment-related surgical HL or both determine prognosis and QoL after CP. De Vile et al. (28) first reported on the association between gross-total resection and adverse long-term outcome in CP patients. The Necker group at Paris, France, (29, 30) developed an algorithm for neurosurgical treatment of CP patients, recommending a risk-adapted hypothalamus-sparing surgical strategy based on a novel MRI-based grading system of presurgical HI (29). The authors (30) could show that CP patients surgically treated according to their hypothalamus-sparing approach presented with similar relapse and progression rates and a lower rate of morbid obesity when compared with their historical cohort of CP patients treated by gross-total resection (28% versus 54%, respectively) (30). This was the first report, proving efficacy of a hypothalamus-sparing surgical (HSS) approach by comparing CP patient cohorts treated by the same experienced neurosurgical team at a single center, and thus minimizing potential bias of surgical experience on outcome analyses. But validation of this observation in a prospective multicenter setting is still missing. Notably, this HSS strategy increased the rate of "normal" BMI from 17 to 38%. However, the percentage of clinically relevant weight gain
remained 62% with nearly 50% of all CP patients developing morbid obesity during follow-up. Furthermore, the mean number of surgical interventions per patient, used as a surrogate for the local recurrence rate, was not noticeably different between the two groups (1.45 in the ERS group and 1.52 in the HSS group). However, follow-up was markedly shorter in the HSS group (mean, 33 months) when compared with the historical group treated by gross-total resection (mean, 103 months). We previously analyzed effects of risk-adapted treatment strategies on outcome after CP based on pre and post-surgical grading of HI and HL in MRI (17, 18, 31, 32). Tumor location and hypothalamic damage with regard to mammillary bodies is essential for our grading of anterior or a+pHI and HL. Based on multivariate risk analysis including initial preoperative HI and surgical HL, presurgical HI was reported to be the major independent risk factor for the development of morbid obesity in CP regardless of chosen surgical strategy and degree of surgical HL (17).

In previous studies on our KRANIOPHARYNGEOM 2007 cohort, we reported on short-term QoL with regard to growth hormone substitution (32) and the concordance between surgical and neuro-radiological assessment of HI and HL (31). In the current study, we analyzed CP patients recruited in KRANIOPHARYNGEOM 2007 with presurgical a+pHI, i.e. patients at high risk for hypothalamic syndrome, in terms of outcome with regard to surgical HL. Notably, radical surgical approaches in these patients resulting in a+pHL were associated with lower relapse/progression rates and highest PFS. Furthermore, when adjusted for irradiation, a higher PFS was observed for non-irradiated patients with a+pHL. These differences were smaller in a non-adjusted comparison of the total, irradiated and non-irradiated subgroups. Notably, patients without HL had the highest rates of radiation because they were frequently treated with an upfront strategy of conservative surgery and radiation therapy. While the patients were treated at many institutions, it seems fairly clear that this was an intentional strategy. Accordingly, we recommend to include radiooncological treatment options in multidisciplinary strategies aiming at hypothalamus-sparing approaches (7, 13, 30, 33-35)

However, patients with surgical a+pHL due to radical gross-total resection presented with significantly higher BMI SDS and decreased QoL scores at all time points during follow-up when compared with CP not suffering from surgical lesions extending to posterior hypothalamic structures. Notably, limited HL confined to anterior hypothalamic structures had similar, i.e. no clinically severe, adverse effect on
weight development and QoL, when compared to patients without HL. The timing of decline in QoL scores (after 1 year from surgery) also merits emphasis, as this could guide parental counselling and supportive efforts by the healthcare system.

Functional capacity was not impaired with regard to HL. We speculate that impairments of functional capacity are most likely to occur during further long-term follow-up of patients with or without HL, which will be analyzed in future studies on this cohort.

The results of our study also provide novel insights into the course of disease. As previously reported (36-39), CP patients at risk for hypothalamic syndrome and severe obesity typically present with significant increase of weight during the first year after diagnosis/surgery and BMI reaches a plateau of severe obesity without further increase during long-term follow-up, i.e. weight increase in the a+pHL group occurred during the first year after surgery, but not afterwards (7). Based on our observation, this typical pattern in course of disease is associated with specific clinical risk factors.

Neither preoperative HI nor anterior surgical HL seems to predispose for significant early weight gain during the first year after CP diagnosis, but specific posterior HL are observed to have causative impact. Accordingly, the current recommendation of hypothalamus-sparing surgery should be more specifically focused on a “posterior hypothalamus-sparing” strategy.

In our study, the occurrence of surgical posterior HL was not related to surgical center size, as presurgical HI and surgical HL were evenly distributed over neurosurgical centers of different center size. This might indicate a current shift towards limited, hypothalamus-sparing surgical strategies when compared to earlier reports in the literature (33).

It is well known that HL can cause severe dysregulation of body composition and energy expenditure at several levels, resulting in hypothalamic syndrome characterized by fatigue, decreased sympathetic tone, decreased energy expenditure and physical activity, hyperphagia, decreased satiety, as well as severe obesity (38, 40-48). Hypothalamic nuclei with posterior location such as dorsomedial nucleus (DMN), dorsal hypothalamic area nucleus (DHA), and ventromedial nucleus (VMN) are key regulators for thermoregulation and locomotion mediating leptin-induced sympathetic activation of brown adipose tissue and energy expenditure (47). Studies in a rodent model for lesion-induced hypothalamic obesity showed that mainly lesions affecting these posterior hypothalamic nuclei were...
associated with the classical phenotype of hypothalamic obesity (49). Roth et al. (47) confirmed these observations in an imaging study on patients with different sellar masses, analyzing location of HL and association with patient outcome.

Due to rareness of the disease the cohort size of our study is limited. Nevertheless, we are reporting on the – to our knowledge – largest specific subgroup of CP patients initially presenting with severe a+pHI. As a limitation, our preoperative image grading system has not been validated yet, which is the aim of future studies. Furthermore, the MRIs depicted in Figure 1 are not adequate to fully illustrate how neuro radiological reference assessment of HL was performed.

Whereas survival rates, BMI development and functional capacity could be assessed with a high grade of completeness during follow-up, QoL analysis was limited to a subgroup of 55 CP patients, for who complete data sets for self and parental-rated PEDQOL scores were available. Increasing patient numbers and prolonging follow-up for assessment of long-term outcome are goals of future studies.

In conclusion, our current study analyzes a large cohort of CP patients at special risk for hypothalamic obesity due to presurgical HI and shows that posterior hypothalamus-sparing strategies prevent QoL impairments and ameliorate development of obesity in this subgroup. Effects of preoperative HI as apriori risk factor for adverse outcome can be modified by risk-adapted surgical strategies aiming at prevention of further posterior HL. Limited surgical HL confined to anterior hypothalamic structures result in minor adverse effects, whereas posterior HL are clinically relevant risk factors for the development of hypothalamic syndrome. Neither pre-operative HI nor postoperative anterior HL are associated with early weight gain. As such, the goals of the surgical approach are critical and should aim specifically to avoid posterior hypothalamic damage. However, hypothalamus-sparing surgical strategies are also associated with higher risk for relapse and progression of residual tumor. Radiooncological therapy is effective in treatment and prevention of relapse/progression and therefore plays an important role in hypothalamus-sparing treatment strategies for CP (1). Standardization of preoperative and postoperative staging is recommended for multidisciplinary decision on risk-appropriate treatment strategy in childhood-onset CP (50).
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**Conflict of interest:** The authors have no conflict of interest to be disclosed

**Authorship:** A.B. researched the data and wrote the manuscript. S.B. conducted and supervised multicenter data collecting and reviewed/edited the manuscript. M.W.-M. performed neuroradiological reference assessments, participated in data analyses, and reviewed/edited the manuscript. G.C. performed PEDQOL data analyses on QoL, participated in data analyses, and reviewed/edited the manuscript. M.E. advised statistical data analyses, and reviewed/edited the manuscript. H.L.M. initiated and conducted the multicenter trials Hit-Endo KRANIOPHARYNGEOM 2000/2007, contributed to the analytical plan and discussion and reviewed/edited the manuscript.

**Ethical standards**

All procedures performed in our study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the local standing committee on ethical practice (Würzburg University, Germany, 94/06) and written parental and/or patient consent was obtained in all cases.

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Figure legends

Figure 1
Presurgical (Figure 1 A, C, E) and postsurgical (Figure 1 B, D, F) MRIs of 3 childhood-onset craniopharyngioma (CP) patients recruited in KRANIOPHARYNGEOM 2007 with initial preoperative anterior and posterior (a+p) hypothalamic involvement graded as previously described (17, 18). In case 1A, no hypothalamic lesions (HL) were detectable on postsurgical MRI after cystic drainage via an inserted catheter (Figure 1B). In case 1C, HL of the anterior hypothalamus (marked with X) were detectable on postsurgical MRI (Figure 1D). In case 1E, HL of the a+p hypothalamus (marked with XX) were detectable on postsurgical MRI (Figure 1F).

Figure 2
Kaplan-Meier analyses of progression-free survival (PFS) rates in childhood-onset craniopharyngioma (CP) patients, recruited with primary involvement of anterior and posterior (a+p) hypothalamus in KRANIOPHARYNGEOM 2007, with regard to degree of surgical resection (Figure 2A; n=97), surgical hypothalamic lesions (HL) graded as previously described (17, 18) (Figure 2B; n=109): No HL; HL of the anterior hypothalamus not involving mammillary bodies and hypothalamic areas dorsal of mammillary bodies; and HL of a+p hypothalamic areas, i.e. involving mammillary bodies and areas dorsal of mammillary bodies. Figure 2C depicts PFS with regards to hypothalamic lesions in non-irradiated CP patients with a+pHL (n=80).

Figure 3
Weight development in 109 childhood-onset craniopharyngioma (CP) patients, recruited with primary involvement of anterior and posterior (a+p) hypothalamus in KRANIOPHARYNGEOM 2007, with regard to surgical hypothalamic lesions (HL) graded as previously described (17, 18): No HL; HL of the anterior hypothalamus not involving mammillary bodies and hypothalamic areas dorsal of mammillary bodies; and HL of a+p hypothalamic areas, i.e. involving mammillary bodies and areas dorsal of mammillary bodies. Body mass index (BMI) SDS (16) is shown at time of diagnosis and at
three intervals after diagnosis (one and 3 years after diagnosis, last visit). White boxes: BMI SDS at diagnosis; hatched boxes: BMI SDS at one year follow-up; gray boxes: BMI SDS at 3 years follow-up, and black boxes: BMI SDS at last visit. The horizontal line in the middle of the box depicts the median. The top and bottom edges of the box respectively mark the 25th and 75th percentiles. Whiskers indicate the range of values that fall within 1.5 box-lengths.

**Figure 4**

Self-assessment (Fig. 4 A, B) and parental assessment (Fig. 4 C, D) of quality of life by Pediatric Quality of Life questionnaire (PEDQOL) in 55 childhood-onset craniopharyngioma (CP) patients, recruited with primary involvement of anterior and posterior hypothalamus in KRANIOPHARYNGEOM 2007, with regard to surgical hypothalamic lesions (HL) graded as previously described (17, 18). White boxes: no HL, hatched boxes: anterior HL, and black boxes: anterior plus posterior HL. PEDQOL scores are shown as negative rating at the time points one year (Fig. 4 A, C) and three years (Fig. 4 B, D) after CP diagnosis. The horizontal line in the middle of the box depicts the median. The top and bottom edges of the box respectively mark the 25th and 75th percentiles. Whiskers indicate the range of values that fall within 1.5 box-lengths.

**Figure 5**

Functional capacity as quantified by German daily life ability scale Fertigkeitenskala Münster-Heidelberg (FMH) in 109 childhood-onset craniopharyngioma (CP) patients, recruited with primary involvement of anterior and posterior (a+p) hypothalamus in KRANIOPHARYNGEOM 2007, with regard to surgical hypothalamic lesions (HL) graded as previously described (17, 18): No HL; HL of the anterior hypothalamus not involving mammillary bodies and hypothalamic areas dorsal of mammillary bodies; and HL of a+p hypothalamic areas, i.e. involving mammillary bodies and areas dorsal of mammillary bodies. FMH scores are shown at time of diagnosis and at three intervals after diagnosis (one and 3 years after diagnosis, last visit). White boxes: FMH at diagnosis; hatched boxes: FMH at one year follow-up; gray boxes: FMH at 3 years follow-up, and black boxes: FMH at last visit. The horizontal line in the middle of the box depicts the median. The top and bottom edges of the box
respectively mark the 25th and 75th percentiles. Whiskers indicate the range of values that fall within 1.5 box-lengths.
Figure 2

A

Complete resection  Incomplete resection

Progression-free survival

\( p = 0.023 \)

Number at risk

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B

NoHL  AnteriorHL  Anterior+posteriorHL

Progression-free survival

\( p = 0.1 \)

Number at risk

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C

NoHL  AnteriorHL  Anterior+posteriorHL

Progression-free survival

\( p = 0.0058 \)

Number at risk

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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation (years)</td>
<td>15</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>24</td>
<td>19</td>
<td>15</td>
<td>3</td>
</tr>
</tbody>
</table>
Figure 3

Body mass index (BMI) SDS

Surgical hypothalamic lesion (HL)

n = 22 19 22 22 27 24 26 28 54 50 43 48

p = 0.012 0.001 0.001 0.007 0.001 0.000 0.000 0.000 0.000 0.000 0.000 0.000
Figure 5

$P = \text{n.s.}$

Surgical hypothalamic lesion (HL)

FMH ability scale (percentile)

n = 12, 13, 18, 22, 16, 21, 22, 26, 40, 31, 30, 49
## Table 1

Distribution of 169 childhood-onset craniopharyngioma (CP) patients recruited in KRANIOPHARYNGEOM 2007 and neurosurgically treated at 63 neurosurgical institutions with different patient load per 7 years recruitment period in KRANIOPHARYNGEOM 2007. S, small-sized centers (n=34): one CP patient per 7 years; M, middle-sized centers (n=21): 2–5 CP patients per 7 years; and L, large-sized centers (n=8): >5 CP patients per 7 years recruitment period. Different degrees of primary presurgical involvement of anterior or anterior plus posterior hypothalamic areas are shown in table lines. Different degrees of surgical hypothalamic lesions (HL) graded as previously described are shown in table columns (17, 18).

<table>
<thead>
<tr>
<th>Neurosurgical center size</th>
<th>Surgical hypothalamic lesions (HL) post OP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No HL</td>
</tr>
<tr>
<td></td>
<td>S</td>
</tr>
<tr>
<td>S</td>
<td>No HI</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>No HI</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>L</td>
<td>No HI</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>51</td>
</tr>
</tbody>
</table>
Table 2

Characteristics in 109 childhood-onset craniopharyngioma (CP) patients, recruited with primary presurgical involvement of anterior+posterior hypothalamus in KRANIOPHARYNGEOM 2007, with regard to surgical hypothalamic lesions (HL), graded as previously described (17, 18). In case of categorical variables, the p-value is calculated based on the sample with non-missing information.

<table>
<thead>
<tr>
<th></th>
<th>Total cohort</th>
<th>No HL</th>
<th>Anterior HL</th>
<th>Anterior + posterior HL</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n (%)</td>
<td>109 (100)</td>
<td>23 (21)</td>
<td>29 (27)</td>
<td>57 (52)</td>
<td></td>
</tr>
<tr>
<td>Gender (female / male)</td>
<td>52 / 57</td>
<td>12 / 11</td>
<td>11 / 18</td>
<td>29 / 28</td>
<td>n.s.</td>
</tr>
<tr>
<td>Age at diagnosis (yrs)</td>
<td>9.6 (1.3 – 17.9)</td>
<td>9.1 (1.3 – 16.6)</td>
<td>10.1 (1.6 – 17.9)</td>
<td>9.7 (1.4 – 17.6)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Age at study (yrs)</td>
<td>16.4 (4.6 – 28.0)</td>
<td>16.3 (6.2 – 23.1)</td>
<td>16.8 (5.1 – 28.0)</td>
<td>16.1 (4.6 – 23.8)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Follow-up interval (yrs)</td>
<td>6.1 (3.0 – 10.2)</td>
<td>6.0 (3.0 – 10.2)</td>
<td>6.4 (3.0 – 10.2)</td>
<td>6.1 (3.1 – 10.2)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Tumor size (cm²)</td>
<td>4.0 (0.3 – 34.6)</td>
<td>5.2 (1.3 – 18.1)</td>
<td>3.7 (0.3 – 32.1)</td>
<td>4.1 (0.5 – 34.6)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Degree of resection, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Incomplete resection</td>
<td>77 (71)</td>
<td>18 (78)</td>
<td>28 (97)</td>
<td>31 (54)</td>
<td></td>
</tr>
<tr>
<td>Complete resection</td>
<td>20 (18)</td>
<td>/</td>
<td>/</td>
<td>20 (35)</td>
<td></td>
</tr>
<tr>
<td>n.a.</td>
<td>12 (11)</td>
<td>5 (22)</td>
<td>1 (3)</td>
<td>6 (11)</td>
<td></td>
</tr>
<tr>
<td>Surgical approach, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Transcranial approach</td>
<td>62 (57)</td>
<td>8 (34)</td>
<td>16 (55)</td>
<td>38 (67)</td>
<td></td>
</tr>
<tr>
<td>Transsphenoidal approach</td>
<td>8 (7)</td>
<td>2 (9)</td>
<td>5 (17)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Stereotactic cyst drainage</td>
<td>2 (2)</td>
<td>2 (9)</td>
<td>/</td>
<td>/</td>
<td></td>
</tr>
<tr>
<td>Open cyst drainage</td>
<td>3 (3)</td>
<td>2 (9)</td>
<td>1 (3)</td>
<td>/</td>
<td></td>
</tr>
<tr>
<td>n.a.</td>
<td>34 (31)</td>
<td>9 (39)</td>
<td>7 (24)</td>
<td>18 (31)</td>
<td></td>
</tr>
<tr>
<td>Irradiation (%)</td>
<td>47 (48)</td>
<td>16 (73)</td>
<td>15 (56)</td>
<td>16 (32)</td>
<td>0.004</td>
</tr>
<tr>
<td>No irradiation</td>
<td>52 (53)</td>
<td>6 (27)</td>
<td>12 (44)</td>
<td>34 (68)</td>
<td></td>
</tr>
<tr>
<td>Age at Irradiation (yrs)</td>
<td>10.7 (2.5 – 18.7)</td>
<td>9.6 (4.0 – 18.7)</td>
<td>12.7 (2.5 – 18.7)</td>
<td>10.4 (7.1 – 16.5)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Interval after dgx</td>
<td>0.9 (0.3 – 5.3)</td>
<td>0.6 (0.3 – 4.1)</td>
<td>0.9 (0.4 – 5.3)</td>
<td>1.2 (0.3 – 4.6)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Gamma knife treatment</td>
<td>1 (1)</td>
<td>/</td>
<td>/</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Photon irradiation</td>
<td>23 (23)</td>
<td>12 (55)</td>
<td>5 (19)</td>
<td>6 (12)</td>
<td></td>
</tr>
<tr>
<td>Proton beam therapy</td>
<td>23 (23)</td>
<td>4 (18)</td>
<td>10 (37)</td>
<td>9 (18)</td>
<td>0.05</td>
</tr>
<tr>
<td>n.a.</td>
<td>10 (9)</td>
<td>1 (4)</td>
<td>2 (7)</td>
<td>7 (12)</td>
<td></td>
</tr>
</tbody>
</table>
Table 3

Hypothalamic-pituitary endocrine deficiencies at last visit in childhood-onset craniopharyngioma patients (n), recruited with primary presurgical involvement of anterior+posterior hypothalamus in KRANIOPHARYNGEOM 2007, with regard to surgical hypothalamic lesions (HL), graded as previously described (17, 18) and irradiation (XRT). The p values refer to comparisons between the hypothalamic lesion subgroups within the context of whether or not the patient received XRT HL=hypothalmic surgical lesion; ant = anterior; post = posterior.

<table>
<thead>
<tr>
<th></th>
<th>total cohort</th>
<th>no HL</th>
<th>ant HL</th>
<th>ant + post HL</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no XRT</td>
<td>XRT</td>
<td>no XRT</td>
<td>XRT</td>
<td>no XRT</td>
</tr>
<tr>
<td>Diabetes insipidus centralis, n</td>
<td>43</td>
<td>35</td>
<td>3</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Growth hormone deficiency, n</td>
<td>33</td>
<td>27</td>
<td>5</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Hypothyroidism, n</td>
<td>41</td>
<td>39</td>
<td>5</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Hypocortisolism, n</td>
<td>40</td>
<td>35</td>
<td>3</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Hypogonadism, n</td>
<td>15</td>
<td>17</td>
<td>2</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>