Surgical Treatment of Craniopharyngiomas in Adults: Comparison between Primary Surgery and Surgery for Recurrence

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[Abstract] Objective: Few studies have investigated the differences in outcomes between primary and repeat surgery for a craniopharyngioma in adults. As a result, a treatment concept for adult patients with a craniopharyngioma has not yet been established. The present study aimed to retrospectively analyze adult patients with craniopharyngioma to compare surgical outcomes between primary surgery and surgery for recurrence. **Methods:** The demographic and clinical data of 68 adult patients with craniopharyngioma who had primary surgery (n=50) or surgery for recurrence (n=18) were retrospectively analyzed. In addition, the patients were followed up for an average of 38.6 months (range: 1–133 months). **Results:** The cohorts of patients undergoing primary surgery or repeat surgery did not differ preoperatively in terms of demographic data, or radiological tumor features. However, patients with recurrent craniopharyngioma had significantly more pituitary hormone deficits and hypothalamo-pituitary disorders before surgery compared with patients with newly diagnosed craniopharyngioma. The success rate of complete resection in primary surgery was 53.2%. Even after repeat surgery, a satisfactory rate of complete resection of 35.7% was achieved. Operative morbidity was increased neither in patients with repeat surgery compared with those with primary surgery (postoperative bleeding P=0.560; meningitis P=1.000; CSF leak P=0.666; visual disturbance P=0.717) nor in patients with complete resection compared with those with partial resection. We found no difference in recurrence-free survival between initial surgery and repeat surgery (P=0.733). The recurrence rate was significantly lower after complete resection (6.9%) than after partial resection (47.8%; P<0.001). **Conclusion:** Attempting complete resection is justified for not only those with newly diagnosed craniopharyngioma but also for those with recurrent craniopharyngioma. However, the surgeon must settle for less than total resection if postoperative morbidity is anticipated.

Key words: craniopharyngioma; adulthood; transcranial; transsphenoidal; primary surgery; recurrence; recurrence-free survival

Craniopharyngiomas (CPs) are rare benign tumors for which treatment is challenging due to their proximity to important vascular and neural structures. Their infiltrative and adhesive growth, as well as their tendency to recur, remains difficult challenges in surgical treatment despite advanced neurosurgical techniques. In particular, the risk of damage to the hypothalamus and its nuclei with the consequences of hypothalamic syndrome limit the radicality of tumor removal[1–4]. Despite the benign histopathological features of CPs, tumor recurrence and hypothalamic dysfunction have a marked impact on the long-term outcomes of CP patients. The established therapeutic options for the treatment of CPs are neurosurgery and radiotherapy (RT)[5]. Due to the documented postoperative deterioration in the quality of life of patients, mainly due to hypothalamic disturbances, a conservative treatment approach with low-risk surgery to avoid hypothalamic damage, followed by postoperative RT, is often advocated for CP treatment in children and adolescents[5–7]. Because few studies specifically address CP in adults[8–10], little is known about the specific characteristics of CPs in adulthood. Consequently, no uniform treatment concepts for adult CP patients have been established. Furthermore, few studies have focused on the difference between initially diagnosed and recurrent CPs in adults. Therefore, the aim of this study was to characterize CPs in adults using a consecutive surgical series from a single center, focusing on the comparison between primary surgery and surgery for recurrence, and to contribute

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to improving the future treatment of adult CP patients.

1 SUBJECTS AND METHODS

We performed a retrospective monocentric cohort study based on the analysis of clinical, endocrinological, imaging, and surgical data in adult CP patients. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the University of Tübingen (reference number 014/2016B02). Patient consent was waived with approval of the Ethics Committee of our University due to the retrospective nature of the cohort study.

1.1 Subjects

Between January 2005 and March 2020, a total of 68 adult CP patients (older than 16 years) were surgically treated in the Department of Neurosurgery at the University Hospital in Tübingen, Germany. In 50 patients ("primary surgery group"), CP was first diagnosed and the first operation was performed in our clinic. Other therapeutic modalities had not yet been performed in these patients. Eighteen patients ("repeat surgery group") presented to us because of tumor progression or a recurrent tumor and had already undergone surgery and/or RT at other hospitals.

1.2 Clinical Evaluation

The standardized questionnaire of the German Craniopharyngioma Register in adults was used to collect the clinical data (UKE NCH–Craniopharyngioma Case Report Form V 1.0). For all patients, demographic data (sex and age), anthropometric data (body weight, height, and BMI), symptoms (headache, weight gain, visual field loss, reduced visual acuity, neurological abnormalities, hypothalamic syndrome, and behavioral abnormalities), endocrinological findings (laboratory chemistry determination), imaging data (preoperative and postoperative MRI and, if applicable, preoperative CT), and surgical data (access route used, resection extent, and postoperative complications in the first 30 days after surgery) were collected and evaluated. In the repeat surgery group, the preoperative data are from the time of presentation at our clinic before reoperation. The data were obtained from the digital patient files.

According to our hospital protocol, the pituitary hormone levels were determined in a standardized manner on the day before the operation and on the fifth postoperative day in the Central Laboratory of the University Hospital. The basal values of cortisol, prolactin, growth hormone (GH), insulin-like growth factor 1, luteinizing hormone, follicle-stimulating hormone, free triiodothyronine, free thyroxine, thyroid-stimulating hormone, and, depending on sex, testosterone or estradiol were examined. Preoperatively, the hormone data obtained by external endocrinologists were also used for the assessment.

Based on the neuroradiological examinations, the approximate volumes of the tumors before surgery were calculated using the diameters according to the formula for the volume of an ellipsoid (0.5236×max. average anterior-posterior×max. average craniocaudal×max. average right-left).

1.3 Follow-up Evaluations

The first follow-up took place 3–6 months after surgery, with annual follow-up examinations thereafter. The relevant time points for the evaluation were the first follow-up after surgery ("early outcome") and the last follow-up ("late outcome"). For patients who had recurrence or progression of CP postoperatively, the data from the time of readmission due to recurrence or progression were also used for the survey. The patients were asked to bring hormone results from their endocrinologist, ophthalmological examinations, and current MRI examinations to the follow-up visits at our clinic. If the examinations were not available, they were carried out as part of the follow-up examinations during our pituitary consultation. The average follow-up time was 38.6 months (range: 1–133 months).

1.4 Patient Status

Patients were divided into five groups based on the patient status during the observation period. Patients without imaging evidence of a residual tumor who had complete tumor removal described in the surgical report were assigned the status "complete remission". The "partial remission" group contained the patients in whom a residual tumor was found in postoperative imaging, but it did not increase in size during the follow-up. If imaging showed recurrence or progression, the patients were assigned to the "recurrence" or "progression" group, respectively. Lastly, the deceased patients whose cause of death was related to the tumor surgery were documented with the status "death".

1.5 Statistical Analysis

Data were statistically analyzed using the Statistical Package for the Social Sciences, version 27. The significance level was set at 5% for all tests (α=0.05). Comparisons of the two groups ("primary surgery" and "repeat surgery") were performed using Pearson's chi-squared test, Fisher's exact test, or the nonparametric Mann-Whitney *U* test. For quantitative characteristics (age, number of pituitary axis insufficiencies, and tumor size), statistical testing for normal distribution was performed using the Kolmogorov-Smirnov test. Non-normally distributed data were tested for statistically significant distributions using the nonparametric Mann-Whitney *U* test. The effect of surgery on symptoms (nonhormonal *vs*. hormonal) was evaluated by comparing symptoms preoperatively *vs*. postoperatively (early outcome as well as late outcome) using the Wilcoxon test and the

McNemar test for paired samples. Survival curves were generated to assess recurrence-free or progression-free survival, and comparisons between the two groups of patients were performed using the log rank test. Where appropriate, the hazard ratio was calculated using Cox regression. Only information that was specifically mentioned in the patient records was used for statistical analysis. If, for example, headache or eating disorders were not mentioned, the symptoms were assessed as missing values.

2 RESULTS

2.1 Patient Presentation

The demographic and clinical data for the entire patient cohort (n=68) in the primary surgery group (n=50), and the repeat surgery group (n=18) are shown in table 1. Visual disturbances were the most common symptom both in patients with newly diagnosed CP and in those with recurrent CP. Advanced obesity was present almost exclusively in the patient group with recurrent CP (table 1). The number of deficient hormone axes was statistically significantly greater in the recurrent CP patients than in those with a primary diagnosis (P<0.001). The radiological characteristics at presentation are shown in table 2. Surprisingly, we found no statistically significant differences in the degree of radiological hypothalamic compression (P=0.552) or tumor size (P=0.533) across patients in different BMI categories before surgery.

2.2 Surgical Approach

In 41 patients (60.3%), the surgery was performed via an open microscopic (±endoscopic) transcranial (TC) approach; while in 17 patients (25%), it was performed via a microscopic (±endoscopic) transsphenoidal (TS) approach. The microsurgical TC approach was the favored access route in both patients with initial CP surgery and those undergoing reoperation (table 3). Among the microscopic (±endoscopic) TC access routes, a pterional approach (23/41) was performed most frequently, followed by median subfrontal/supraorbital (7/41) and frontolateral (6/41) approaches. There was no statistically significant difference between the two patient groups ("primary surgery" and "repeat surgery") in the frequencies of accesses performed (table 3).

Table 1 Demographic and clinical data prior to primary or repeat surgery in 68 adult patients with craniopharyngioma

	Total cohort *n* (%)	Primary surgery *n* (%)	Repeat surgery *n* (%)	*P*
Demographic data				
Age (years)	43.87 (16–83)[#]	46.12 (16–83)[#]	37.61 (18–59)[#]	0.128[a]
Sex				0.618[b]
Male	42 (61.8%)	30 (60%)	12 (33.3%)	
Female	26 (38.2%)	20 (40%)	6 (66.7%)	
Clinical data				
BMI				0.148[a]
Underweight (<18.5)	1/68 (1.5%)	1/50 (2%)	0/18 (0%)	
Normal weight (18.5–24.9)	23/68 (33.8%)	18/50 (36%)	5/18 (27.8%)	
Overweight (25–29.9)	25/68 (36.8%)	19/50 (38%)	6/18 (33.3%)	
Obesity class Ⅰ (30–34.9)	10/68 (14.7%)	9/50 (18%)	1/18 (5.6%)	
Obesity class Ⅱ (35–39.9)	4/68 (5.9%)	1/50 (2%)	3/18 (16.7%)	
Obesity class Ⅲ (≥ 40)	5/68 (7.4%)	2/50 (4%)	3/18 (16.7%)	
Neurological disorder	14/67 (20.9%)	11/49 (22.4%)	3/18 (16.7%)	0.743[c]
Headache	33/62 (53.2%)	26/47 (55.3%)	7/15 (46.7%)	0.559[b]
Objective visual impairment				
Visual field defect	44/64 (68.8%)	31/47 (66%)	13/17 (76.5%)[†]	0.423[b]
Visual acuity reduction	37/65 (56.9%)	26/48 (54.2%)	11/17 (64.7%)[†]	0.451[b]
Behavioral problems	2/63 (3.2%)	2/49 (4%)	0/14 (0%)	1.000[c]
Hypothalamic syndrome				
Eating disorder or morbid obesity	8/64 (12.5%)	5/48 (10.4%)	3/16 (18.8%)	0.401[c]
Sleep disturbance	6/64 (9.4%)	4/48 (8.3%)	2/16 (12.5%)	0.635[c]
Temperature fluctuation	0/64 (0%)	0/48 (0%)	0/16 (0%)	
Incidental finding	9/68 (13.2%)	9/50 (18%)	0/18 (0%)	0.099[c]
Pituitary dysfunction				
Diabetes insipidus	15/64 (23.4%)	6/46 (13%)	9/18 (50%)	0.003[*c]
Secondary hypothyroidism	31/66 (47.0%)	16/48 (33.3%)	15/18 (83.4%)	<0.001[*b]
Growth hormone deficiency	26/66 (39.4%)	13/48 (27.1%)	13/18 (72.2%)	0.001[*b]
Hypocortisolism	32/66 (48.4%)	15/48 (31.3%)	17/18 (94.4%)	<0.001[*b]
Hypogonadism	39/65 (60.0%)	23/47 (48.9%)	16/18 (88.9%)	0.003[*b]
Hyperprolactinemia	25/64 (39.1%)	19/47 (40.4%)	6/17 (35.3%)	0.710[b]

[#]Mean (Minimum-Maximum); [a]Mann-Whitney *U* test; [b]Pearson's chi-squared test; [c]Fisher's exact test; [*]Statistically significant; [†]new or worsening visual disturbance; BMI: body mass index

Table 2 Radiological characteristics prior to primary or repeat surgery in 68 adult patients with craniopharyngioma

Radiological features	Total cohort *n* (%)	Primary surgery *n* (%)	Repeat surgery *n* (%)	*P*
Tumor localization				0.069[c]
Intrasellar	1/66 (1.5%)	0/48 (0%)	1/18 (5.6%)	
Intra-extrasellar	32/66 (48.5%)	20/48 (41.7%)	12/18 (66.7%)	
Extrasellar	31/66 (46.9%)	26/48 (54.2%)	5/18 (27.8%)	
Intraventricular	2/66 (3.0%)	2/48 (4.2%)	0/18 (0%)	
Tumor structure				0.566[c]
Solid	3/68 (4.4%)	3/50 (6%)	0/18 (0%)	
Cystic	14/68 (20.6%)	10/50 (20%)	4/18 (22.2%)	
Mixed	51/68 (75%)	37/50 (74%)	14/18 (77.8%)	
Calcifications	46/62 (72.2%)	32/45 (71.1%)	14/17 (82.4%)	0.520[b]
Hydrocephalus	15/68 (22.1%)	11/50 (22%)	4/18 (22.2%)	0.611[b]
Compressed structure				
Pituitary stalk	66/68 (97.1%)	48/50 (96%)	18/18 (100%)	1.000[b]
Third ventricle	54/68 (79.4%)	40/50 (90%)	14/18 (77.8%)	1.000[b]
Optic chiasm	63/68 (92.6%)	47/50 (94%)	16/18 (88.9%)	0.602[b]
Anterior hypothalamus	44/68 (64.7%)	35/50 (70%)	9/18 (50%)	0.128[c]
Posterior hypothalamus	22/68 (32.4%)	17/50 (34%)	5/18 (27.8%)	0.628[c]
Tumor size (cm^3)	101.5 (6.58–453.89)[#]	96.65 (11.68–323.65)[#]	113.15 (6.58–453.89)[#]	0.719[a]

[#]Mean (Minimum-Maximum); [a]Mann-Whitney *U* test; [b]Fisher's exact test; [c]Pearson's chi-squared test

2.3 Histological Findings

The histopathological subtype was available for 53 of the 68 CP patients. Only 4 of these 53 cases were of the papillary subtype; while the adamantinomatous subtype clearly predominated, with 49 cases. The presence of BRAF-V600E mutations has been implemented in the histopathological diagnosis of CP to confirm the papillary subtype. We could retrieve residual tumor tissue from 3 of our 4 papillary CPs for retrospective analysis and have confirmed BRAF-V600E mutations in these 3 cases. The distribution of histopathological subtypes did not differ between the patient groups undergoing primary *vs*. repeat surgery (P=0.792).

2.4 Morbidity and Mortality

Bleeding complications occurred in 3 patients after primary surgery, while no patients experienced bleeding after repeat surgery (table 4). One patient suffered a subgaleal and epidural hemorrhage, which was successfully treated conservatively. In the second patient, hemorrhage into the resection cavity occurred, leading to worsening of visual impairment, which completely resolved after revision surgery. The third patient developed an intraventricular and subarachnoid hemorrhage with subsequent vasospasm and cerebral ischemia after initial surgery. He had a severe, protracted course and died four months after surgery because of the disease. This was the only patient who died in association with the surgery (table 5). Another patient with cerebral ischemia suffered a small caudate nucleus infarction from which mild amnesic disturbances remained at the last follow-up.

Of the 7 (10.3%) patients with cerebrospinal fluid (CSF) leakage (4 cases after TS surgery, 2 cases after TC microscopic surgery, and 1 case after transcranial endoscopic surgery), revision surgery was successfully performed on 6 patients. In the seventh case, the insertion of a lumbar drain led to regression of the CSF leak. It is noteworthy that CSF leakage occurred more frequently after initial surgery (table 4).

Among the postoperative complications assessed, we found a statistically significant difference, with a greater frequency after initial surgery than after repeat surgery, only for salt and water balance disorders (table 4). The postoperative salt and water balance disturbances observed were transient diabetes insipidus (DI) in 9 cases, permanent DI in 16 cases, and syndrome of inappropriate antidiuretic hormone (SIADH) secretion in 2 cases. The two patients with SIADH developed seizures in the setting of hyponatremia.

Table 3 Surgical approaches

Surgical approach	Total cohort *n* (%)	Primary surgery *n* (%)	Repeat surgery *n* (%)	*P*
				0.287[a]
TC Micro	39/68 (57.4%)	28/50 (56%)	11/18 (61.1%)	
TS	15/68 (22.1%)	12/50 (24%)	3/18 (16.7%)	
TC Micro + Endo	2/68 (2.9%)	2/50 (4%)	0/18 (0%)	
TS Micro + Endo	2/68 (2.9%)	1/50 (2%)	1/18 (5.6%)	
TC Endo	5/68 (7.4%)	5/50 (10%)	0/18 (0%)	
Stereotactic puncture	4/68 (5.9%)	2/50 (4%)	2/18 (11.1%)	
Combined	1/68 (1.5%)	0/50 (0%)	1/18 (5.6%)	

[a]Pearson's chi-squared test; TC: transcranial approach; TS: transsphenoidal approach; Micro: microscopic; Endo: endoscopic

Table 4 Postoperative complications

Postoperative complication	Total cohort *n* (%)	Primary surgery *n* (%)	Repeat surgery *n* (%)	*P*
Bleeding	3/68 (4.4%)	3/50 (6%)	0/18 (0%)	0.560[a]
Meningitis	5/68 (7.4%)	4/50 (8%)	1/18 (5.6%)	1.000[a]
CSF leak	7/68 (10.3%)	6/50 (12%)	1/18 (5.6%)	0.666[a]
Visual disturbance	10/68 (14.7%)	7/50 (14%)	3/18 (16.7%)	0.717[a]
Disturbance of salt/water balance	27/67 (40.3%)	25/49 (51%)	2/18 (11.1%)	0.003[*b]
Miscellaneous	15/68 (22.1%)	11/50 (22%)	4/18 (22.2%)	1.000[a]
Other operative complications				
Epistaxis	1/15 (6.7%)	0/11 (0%)	1/4 (25%)	
Seizure	2/15 (13.3%)	2/11 (18.2%)	0/4 (0%)	
Palacos dislocation	1/15 (6.7%)	1/11 (9.1%)	0/4 (0%)	
Oculomotor paresis, transient	2/15 (13.3%)	2/11 (18.2%)	0/4 (0%)	
Ischemia	2/15 (13.3%)	1/11 (9.1%)	1/4 (25%)	
Hydrocephalus	2/15 (13.3%)	1/11 (9.1%)	1/4 (25%)	
Medical complications				
Pneumonia	2/15 (13.3%)	1/11 (9.1%)	1/4 (25%)	
DVT/PE	1/15 (6.7%)	1/11 (9.1%)	0/4 (0%)	
Psychosomatic syndrome	2/15 (13.3%)	2/11 (18.2%)	0/4 (0%)	
Rec. laryngeal nerve palsy	1/15 (6.7%)	1/11 (9.1%)	0/4 (0%)	
Addisonian crisis	1/15 (6.7%)	1 /11 (9.1%)	0/4 (0%)	

[*]Statistically significant; [a]Fisher's exact test; [b]Pearson's chi-squared test; CSF: cerebrospinal fluid; DVT: deep vein thrombosis; PE: pulmonary embolism; Rec: recurrent

Table 5 Early and late outcomes: patient status

	Total cohort *n* (%)	Primary surgery *n* (%)	Repeat surgery *n* (%)	*P*
Early outcome				0.386[a]
Complete remission	30/61 (49.2%)	25/47 (53.2%)	5/14 (35.7%)	
Partial remission	25/61 (41%)	17/47 (36.2%)	8/14 (57.1%)	
Progression	5/61 (8.2%)	4/47 (8.5%)	1/14 (7.1%)	
Recurrence	0/61 (0%)	0/47 (0%)	0/14 (0%)	
Death	1/61 (1.6%)	1/47 (2.1%)	0/14 (0%)	
Late Outcome				0.234[a]
Complete remission	20/38 (52.6%)	18/31 (58.1%)	2/7 (28.6%)	
Partial remission	13/38 (34.2%)	9/31 (29%)	4/7 (57.1%)	
Progression	5/38 (13.2%)	4/31 (12.9%)	1/7 (14.3%)	
Recurrence	0/38 (0%)	0/31 (0%)	0/7 (0%)	
Death	0/38 (0%)	0/31 (0%)	0/7 (0%)	

[a]Mann-Whitney *U* test

Interestingly, there were no statistically significant differences in the typical postoperative complications when comparing patients with partial *vs*. complete resection or when comparing the TC *vs*. TS patient groups. No patient died within the first 30 postoperative days.

The 5 patients who had received RT prior to the operation in our department accounted for a high proportion of postoperative complications (e.g., meningitis, visual disturbance, disturbance of salt/water balance, ischemia, hydrocephalus, and pneumonia). Four of the 5 patients had not only prior RT but also several surgical interventions before the first presentation in our department. Therefore, it remains unclear whether the high complication rate was due to prior RT, prior surgeries, or both.

2.5 Early Outcome

2.5.1 Patient Status Early outcomes were available for 61 patients; 7 patients did not present for follow-up. Complete remission was achieved in 53.2% of the patients through primary surgery (table 5). However, complete remission was also achieved in more than one third of the patients after repeat surgery. We observed early progression in 4 cases (8.5%) after initial surgery and in 1 case (7.1%) after repeat surgery (table 5). In all cases, this was due to an increase in the cystic portion. There was no significant difference in the extent of resection between the two surgical groups (P=0.386).

In 3 cases in the primary surgery group (case number 1, 10, and 14; table 6) and in 3 cases in the repeat surgery group (case number 17, 18, and 21; table 6), early follow-up treatment with reoperation and/or RT was carried out. In 3 of these cases (case number 1, 17, and 18), RT had already been planned as part of the therapeutic strategy before surgery.

2.5.2 Early Clinical Outcome: Nonendocrine Symptoms The early results showed no statistically significant differences in nonendocrine symptoms

Table 6 Cases with progression or recurrence of the tumor during the entire observation period and the follow-up treatment carried out

Case	Operation group	Operation performed	Status	Months after operation	Follow-up treatment	Status at the end of follow-up
1	Primary surgery	Biopsy + cyst release	Partial remission	2	IMRT (48.6/54 Gy) (planned)	Partial remission
2	Primary surgery	Partial resection	Progression	10	Partial resection	Partial remission
3	Primary surgery	Total resection	Recurrence	46	Observation	Stable findings
4	Primary surgery	Partial resection	Progression	27	IMRT (54 Gy)	Partial remission
5	Primary surgery	Partial resection	Progression	18	Stereotactic RT (54 Gy)	Partial remission
6	Primary surgery	Partial resection	Progression	117	Observation	Stable findings
7	Primary surgery	Partial resection	Progression	2	Observation	Partial remission
			Progression	23	Partial resection	
			Progression	108	Cyst release	
8	Primary surgery	Partial resection	Progression	23	Total resection	–
			Recurrence (Metastasis)	49	Total resection	
			Progression	76	Proton-beam RT (50.4 Gy)	
9	Primary surgery	Partial resection	Progression	8	Partial resection + stereotactic RT (54 Gy)	Partial remission
10	Primary surgery	Cyst release	Progression	3	Cyst release	Partial remission
			Partial remission	5	Partial resection + Proton-beam RT	
11	Primary surgery	Cyst release	Progression	11	Cyst release	Complete remission
			Progression	69	Total resection (two-staged)	
12	Primary surgery	Total resection	Recurrence	24	Total resection	Complete remission
13	Primary surgery	Partial resection	Progression	11	Observation	Stable findings
14	Primary surgery	Cyst release	Progression	3	Cyst release + RT (54 Gy)	Partial remission
			Progression	7	Cyst release	
15	Primary surgery	Partial resection	Progression	3	No follow-up	–
16	Primary surgery	Partial resection	Progression	11	Partial resection	Complete remission
			Progression	21	Total resection	
17	Repeat surgery	Partial resection	Partial remission	2	RT (54 Gy) (planned)	–
18	Repeat surgery	Partial resection	Partial remission	2	Stereotactic fractionated RT (54 Gy) (planned)	–
19	Repeat surgery	Partial resection	Progression	7	Cyst release	Partial remission
			Progression	54	Cyst release + RT (54 Gy)	
20	Repeat surgery	Cyst release	Progression	10	Cyst release + RT (50.4 Gy)	Partial remission
21	Repeat surgery	Cyst release	Progression	4	Cyst release	
			Progression	16	Cyst release	–

RT: radiotherapy; IMRT: intensity-modulated radiotherapy

between the patient cohorts with primary surgery *vs*. repeat surgery (table 7). Only in the cohort undergoing primary surgery was there a significant increase in the body mass index (BMI) at the first postoperative follow-up visit compared with preoperatively (P=0.001; tables 1 and 7). There was a significant improvement in headache with primary surgery (P=0.001; tables 1 and 7). Visual fields were improved statistically significantly after both primary surgery (P<0.01) and repeat surgery (P=0.017; fig. 1).

2.5.3 Early Clinical Outcome: Endocrine Symptoms

We observed a significant increase in the frequency of pituitary dysfunction after surgery in the group of patients undergoing initial surgery. The postoperative increases in hormonal deficits were found to be statistically significant for all hormonal axes except the GH and gonadal axes (DI, P<0.001; secondary hypothyroidism, P=0.039; hypocortisolism, P=0.021; GH deficiency, P=0.727; hypogonadism, P=0.388). The number of insufficient hormonal axes increased in 54.3% of the patients after initial surgery. On the other hand, a decrease in the number of insufficient hormonal axes was observed in 27.3% of the patients after initial surgery (table 8).

Of the total of 42 hormonal axes that showed new insufficiency in the entire sample, 14 were DI (33.3%), 10 were hypocortisolism (23.8%), 8 were hypothyroidism (19.1%), 8 were hypogonadism (19.1%), and 2 were GH deficiency (4.8%). All new axis insufficiencies were found after primary surgery. Among the 15 axis insufficiencies that recovered after surgery, 6 were in the GH axis (40%), 4 were in the gonadal axis (26.7%), 3 were in the adrenocortical axis (20%), and 2 were in the thyroid axis (13.3%). Recovery of a preoperative insufficiency occurred only after primary surgery, with the exception of a single

Table 7 Early and late outcomes: Nonendocrine symptoms

Symptoms	Early outcome			Late outcome		
	Primary surgery *n* (%)	Repeat surgery *n* (%)	*P*	Primary surgery *n* (%)	Repeat surgery *n* (%)	*P*
BMI			0.269[a]			0.620[a]
Underweight (<18.5)	0/35 (0%)	0/6 (0%)		2/23 (8.7%)	0/6 (0%)	
Normal weight (18.5–24.9)	11/35 (31.4%)	1/6 (16.7%)		3/23 (13%)	3/6 (50%)	
Overweight (25–29.9)	13/35 (37.1%)	1/6 (16.7%)		5/23 (21.7%)	1/6 (16.7%)	
Obesity class Ⅰ (30–34.9)	5/35 (14.3%)	1/6 (16.7%)		8/23 (34.8%)	0/6 (0%)	
Obesity class Ⅱ (35–39.9)	3/35 (8.6%)	2/6 (33.3%)		1/23 (4.3%)	0/6 (0%)	
Obesity class Ⅲ (≥40)	3/35 (8.6%)	1/6 (16.7%)		4/23 (17.4%)	2/6 (33.3%)	
Other hypothalamic symptoms						
Eating disorder/morbid obesity	7/31 (22.6%)	2/6 (33.3%)	0.620[b]	4/27 (14.8%)	2/6 (33.3%)	0.295[b]
Somnolence/sleep disturbance	3/30 (10%)	1/5 (20%)	0.477[b]	2/24 (8.3%)	1/5 (20%)	0.446[b]
Temperature fluctuation	0/30 (0%)	0/4 (0%)		0/25 (0%)	0/4 (0%)	
Neurological disorder	5/43 (11.6%)	2/14 (14.3%)	1.000[b]	0/31 (0%)	0/7 (0%)	
Headache	8/39 (20.6%)	2/11 (18.2%)	1.000[a]	1/30 (3.3%)	0/6 (0%)	1.000[b]
Behavioral problems	2/31 (6.5%)	0/4 (0%)	1.000[b]	0/27 (0%)	0/5 (0%)	

[a]Mann-Whitney *U* test; [b]Fisher's exact test

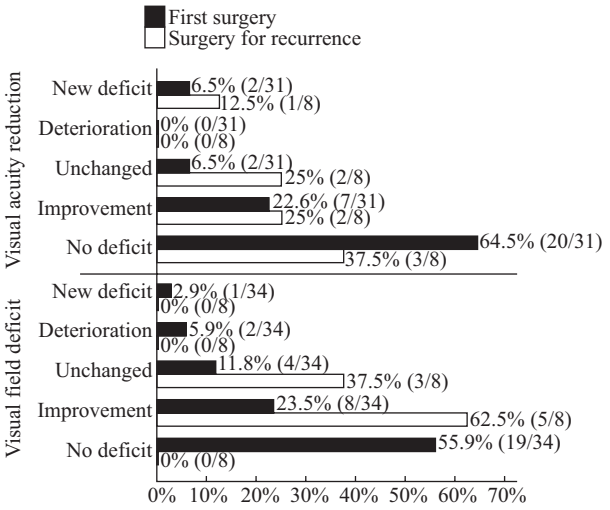

Fig. 1 Effect of surgery on visual disturbances: ophthalmological findings at the early outcome compared with the preoperative status

case with recovery of a GH deficiency after repeat surgery.

2.6 Late Outcome

2.6.1 Patient Status A total of 17 patients received additional treatment during follow-up, including 12 patients after initial surgery and 5 patients after repeat surgery (table 6). Late patient status was available for 38 patients (mean: 58 months after surgery; range: 7–133 months; table 5). Complete remission was found in 58.1% of the patients with primary surgery and 28.6% of the patients with repeat surgery. One patient died approximately 18 months after surgery due to a cause unrelated to CP.

2.6.2 Late Clinical Outcome: Nonendocrine Symptoms Analysis of late outcomes showed no significant differences in nonendocrine symptoms between the cohort of patients with initial surgery and those with repeat surgery (table 7). However, the small number of patients with an available last outcome in

Table 8 Early outcome: Number of new and recovered insufficiencies in individual patients

Early outcome	Total cohort *n* (%)	Primary surgery *n* (%)	Repeat surgery *n* (%)	*P*
Number of new axis insufficiencies				0.009*[a]
No new insufficiency	24/43 (55.8%)	16/35 (45.7%)	8/8 (100%)	
1 new insufficiency axis	7/43 (16.3%)	7/35 (20%)	0/8 (0%)	
2 new insufficiency axes	4/43 (9.3%)	4/35 (11.4%)	0/8 (0%)	
3 new insufficiency axes	5/43 (11.6%)	5/35 (14.3%)	0/8 (0%)	
4 new insufficiency axes	3/43 (7%)	3/35 (8.6%)	0/8 (0%)	
5 new insufficiency axes	0/43 (0%)	0/35 (0%)	0/8 (0%)	
Number of recovered axes				0.357[a]
No recovery	31/41 (75.6%)	24/33 (72.7%)	7/8 (87.5%)	
1 recovered axis	7/41 (17.1%)	6/33 (18.2%)	1/8 (12.5%)	
2 recovered axes	1/41 (2.4%)	1/33 (3%)	0/8 (0%)	
3 recovered axes	2/41 (4.9%)	2/33 (6.1%)	0/8 (0%)	
4 recovered axes	0/41 (0%)	0/33 (0%)	0/8 (0%)	
5 recovered axes	0/41 (0%)	0/33 (0%)	0/8 (0%)	

*statistically significant; [a]Mann-Whitney *U* test

the repeat surgery group should be taken into account when interpreting the results. We observed only minor changes in the ophthalmological status between early outcome and late outcome.

2.6.3 Late Clinical Outcome: Endocrine Symptoms

In the entire sample, new insufficiencies developed in 10 patients in a total of 16 hormonal axes between the early and late outcomes. With one exception, all new axis insufficiencies were in the group with primary surgery. In 7 of these 10 patients (70%) with new axis insufficiencies occurring during follow-up, additional treatment was performed during the observation period. Four patients underwent reoperation, and 3 patients underwent postoperative RT. The other 3 cases were patients who had been in full remission since the first follow-up visit. The only case of new axis insufficiency during the follow-up period in the repeat surgery group occurred after postoperative RT. In 6 patients, one hormonal axis recovered between the first and last follow-up. All of these recoveries were in patients after initial surgery.

2.7 Recurrence Rate and Recurrence-free Survival

During the entire observation period, a total of 18 of 61 patients (29.5%) had progression or recurrence (table 6). True recurrence occurred in only 2 of 29 patients (6.9%) after complete resection, while 11 of 23 patients (47.8%) had tumor progression after partial resection, and 5 of 9 patients (55.6%) who only underwent cyst release suffered tumor progression.

In the group with primary surgery, a total of 15 of 48 cases (31.3%) had progression or recurrence; and in the group with repeat surgery, 3 of 13 cases (23.1%) had progression or recurrence. We found no statistically significant difference in recurrence/progression-free survival between the patient groups with initial *vs*. repeat surgery (P=0.733). The mean time to recurrence/progression was 69 months (95% confidence interval: 48.6–89.1 months) after initial surgery and 83 months (95% confidence interval: 38.1–127.8 months) after repeat surgery. Half of the patients with initial surgery had had recurrence/progression at 46 months after surgery. In the repeat surgery group, all events occurred within the first 12 months after surgery. The recurrence-free survival rates were 93.5% at 2 years, 49.2% at 5 years, and 24.6% at 10 years in the group with primary surgery and 60.6% at 2, 5, and 10 years in the group with repeat surgery (fig. 2). There was a 14-fold increased risk of recurrence after partial tumor resection compared with complete resection (P<0.001).

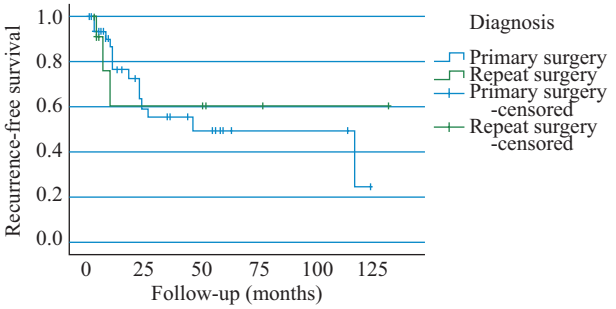

Fig. 2 Recurrence-free survival after primary surgery *vs*. after repeat surgery

3 DISCUSSION

Our results are consistent with those of studies published in the literature, which report that visual impairment is the most common symptom in adult CP patients, with frequencies ranging from 47% to 87.5%[8, 9, 11–17]. In both patients undergoing primary surgery or undergoing repeat surgery, the most common symptom we found was visual impairment.

Compared with patients with initially diagnosed CP, patients with recurrent CP had a high incidence of hypothalamo-pituitary dysfunction prior to repeat surgery, a large proportion of which was presumably due to prior treatment.

Hypothalamic syndrome with obesity is frequently caused by the CP itself. In the series of adults with CP, the incidence of preoperative obesity varied between 13% and 61%[15, 18–21]. Our data describing preoperative overweight in 38% and obesity in 24% of patients in the primary surgery group are in line with the literature. In pediatric patients, hypothalamic syndrome was found in 35% of cases and obesity was found in 12%–19% of cases at the time of diagnosis[3, 5]. These data suggest that the rate of obesity at initial diagnosis is even higher in adult CP patients than in pediatric CP patients. Studies show that these symptoms may predict a deterioration in the quality of life of patients after treatment[6, 15].

The transcranial approach was predominant in our series. In surgery for CP, we mostly used the pterional approach because of its versatility. It provides access through the interoptic window, the opticocarotid triangle, the caroticosylvian window, and to some extent through the lamina terminalis into the third ventricle. In comparison with the frontolateral approach, it allows better exposure to lateral structures such as the oculomotor nerve and to the prepontine area[22].

The interhemispheric median subfrontal approach is favored in third ventricle CP in the absence of hydrocephalus, as it allows bilateral visualization of the third ventricle wall and a deep look into the ventricle. However, the median subfrontal approach has limitations in cases with lateral CP extension and carries a higher risk of olfactory loss. In addition, a transsphenoidal approach was preferred in CP with enlarged sella and a significant intrasellar portion of the CP. Some small suprasellar CPs in the midline were operated using a transtuberculum sellae extension of the TS approach[4, 23–25].

There is a large range of success rates of complete resection reported in the literature: In studies of more than 100 patients that evaluated pediatric and adult patients published between 1990 and 2010, the rate of complete resection ranged from 18% to 90%[1, 12, 20, 26, 27]. In recent studies considering only adults with CP, the rate of complete resection ranged from 30% to 68.8%[8, 12, 13, 15, 28]. The resection rates vary depending on surgical experience as well as on the surgical strategy. The surgical strategy of always performing a complete resection is associated with a high complication rate[29, 30]. As described by Fahlbusch *et al*[1], we attempted a complete resection, but not at any price. Particularly in cases with strong adhesions to vessels and neural structures and in cases with considerable hypothalamic infiltration, we were satisfied with a subtotal or partial resection at our clinic in Tübingen. The low complication rate in our series supports this surgical concept.

According to the literature, complete resection is more difficult to achieve in patients with repeat surgery compared with those undergoing first operations[1, 8, 15]; however, the difference in the complete resection rate between the primary and repeat surgery groups was not statistically significant in our study. In our study, complete resection was achieved in more than one third of cases of repeat surgery, which compares favorably with the literature[15, 31].

In studies on CP in adults published in the past decade, the frequency of postoperative hemorrhage is reported to be 1.3%–8%, the frequency of infection or meningitis is 1.5%–5%, the frequency of cerebral ischemia is 1.3%–5.3%, the frequency of postoperative hydrocephalus is 3.1%–5%, and the frequency of CSF fistula is 2.5%–16.3%[10, 12, 13, 16, 32]. The frequencies of these typical postoperative complications in our series were comparable to those reported in the literature.

It has been described in the literature that surgical treatment for recurrent CP is associated with higher perioperative morbidity and mortality compared with primary surgery[15]. However, there were no significant differences in the typical postoperative complications between primary surgery and repeat surgery in our patient cohort. We even found a tendency toward a higher rate of CSF leakage and postoperative bleeding after primary surgery than after repeat surgery. This finding was not statistically significant, and the differences might disappear with a larger number of cases. In our study, there were no significant differences in the frequency of typical postoperative complications between partial and complete resection. Similarly, other current studies show no differences in complication rates between partial and complete resection[16, 20, 32]. The demonstrated low morbidity and significantly lower risk of recurrence with complete tumor resection confirm our strategy of aiming for complete tumor removal; however, radical removal should not be forced at any cost. Our data show that attempting complete resection is justified for not only primary operations but also repeat operations.

In the literature, 37%–71% of patients are reported to experience an improvement in pre-existing visual disturbance after surgery[9, 13, 15, 17, 31, 33]. We found similar postoperative improvement in both surgical groups in our study. Postoperative weight gain has been reported in up to 50%–70% of cases[2]. This undesirable hypothalamic obesity is associated with not only a poorer quality of life but also increased cardiovascular risk, metabolic syndrome, and, as a result, increased mortality[2, 3]. In our series, obesity was present in 24% of patients before initial surgery and increased to 56.5% at the late outcome, which is consistent with published data in adult CP patients[16, 18, 20, 34]. After repeat surgery, there was already an increase in the rate of obesity from 39% before surgery to 66.7% at the early outcome. Weight gain is particularly severe in the first 3–6 months after surgery. It can be postulated that the surgical procedure leads to irritation of the hypothalamus and early weight gain. Afterward, there is a slowing of weight gain. We postulate that a surgically induced lesion is the cause of the long-term slow weight gain. In some patients, however, body weight can plateau, and in some cases even weight loss can be observed. However, conscious measures by the patients to counteract the increased body weight, such as dietary changes or exercise, can contribute to this. In pediatric patients, hypothalamic syndrome has been reported in 65%–80% of patients after complete resection[5]. Obesity has been reported in 55% of pediatric patients after treatment[3]. Similar to the pediatric series, the prevalence of obesity increased to >50% of patients at the late outcome in our series.

The early outcome data show that more than half of the patients had one or more new insufficient pituitary axes after the primary operation. Our data are comparable to those published in the literature showing a significant increase in hypothalamo-pituitary axis insufficiencies after surgery[13, 15, 16, 19, 31]. Similarly, there was a marked increase in the frequency of DI after surgery in published adult series from 0–26.7% preoperatively to 52.4%–81.3% postoperatively[13, 15, 16, 19, 32, 33].

We found no new axis insufficiencies at the early outcome after repeat surgery, which was due in part to the high rate of axis insufficiencies before surgery. In contrast, Turel *et al* found new insufficiencies after repeat surgery in 44% of cases in their cohort of patients[31]. During the course of further follow-up, new insufficiencies of pituitary hormone axes occurred in one third of the patients after initial surgery and in 14% of patients after repeat surgery. Of great importance is the fact that 70% of the patients with new axis insufficiencies at the late outcome compared with the early outcome had received additional treatment during the follow-up period. Encouragingly, we

observed a recovery of pituitary insufficiencies at the early outcome in one quarter of the patients after initial surgery and in 12% after repeat surgery.

In different cohorts of adult CP patients, the frequencies of recurrence or progression are described to range from 12.2% to 39.1%[8, 13, 15–17, 35]. During the entire observation period, we found recurrence or progression in 29.5% of patients.

The literature reports a recurrence rate of 10%–25% after complete resection[8, 12, 13, 15–17, 35]. In our series, we found a lower recurrence rate (7%) after complete resection. This is likely due to surgical experience and our strict criteria for defining complete resection. The low recurrence rate clearly demonstrates that the goal of complete resection is reasonable. If a complete resection is successful, the patients are free of tumor burden and have a favorable future perspective from a psychological point of view.

In our series, the recurrence rate after incomplete resection was 48%. Consistent with our results, in a recent meta-analysis, the authors found that the recurrence rate was lowest after complete resection: They reported a recurrence rate of 17% after complete extirpation, followed by a recurrence rate of 27% after partial resection with postsurgical RT. The highest recurrence rate of 45% was found after partial resection without postsurgical radiation[8]. In the few studies that specifically address recurrence after initial or repeat surgery in adults with CP, similar recurrence rates for primary and recurrent CP cases are reported. A large series with a total of 153 patients (only 12 of whom were pretreated) by Lopez-Serna *et al* showed a recurrence-free survival rates of 78% at 5 years and 72% at 10 years[12]. Meanwhile, in a cohort consisting exclusively of patients with repeat surgery, Turel *et al* found that 20.6% of the patients experienced relapse or progression during follow-up[31]. In a cohort consisting exclusively of adult patients undergoing initial surgery, Lee *et al* have reported postoperative recurrence-free survival rates of 87% at 5 years and 76.8% at 10 years without postoperative RT[16]. Furthermore, Kim *et al* have reported a recurrence rate of 27% after primary surgery in adults with CP, with recurrence diagnosed at a mean of 89 months after surgery[17].

We found no statistically significant difference in recurrence-free survival between the patient groups undergoing primary *vs*. repeat surgery. Of note, our data indicate a tendency toward even lower recurrence rates following repeat surgery compared with initial surgery.

In total, 5 patients in the primary surgery group and 4 patients in the repeat surgery group underwent RT or were already scheduled for RT. We saw an indication for adjuvant postoperative RT if a significant residual tumor had been left behind. However, the decision was made on an individual basis, and there were some exceptions. For example, some cystic CP patients underwent cyst drainage with insertion of a catheter, thus allowing permanent drainage of the newly formed cyst fluid into the ventricle. In such cases, we abstained from early postoperative RT. If recurrence occurred during follow-up, reoperation was offered if we anticipated a reasonable chance for a total or near-total removal of the CP. Otherwise, the patients were scheduled for either fractionated RT or radiosurgery.

In their systematic review of adults with CP, Cossu *et al* described overall survival rates of 89%–94% at the 5-year follow-up and 85%–90% at the 10-year follow-up[9]. During the entire observation period, only one of our patients died of a cause related to the CP. Thus, the survival rate observed in our series was high compared with the rates reported in the literature. We would like to emphasize that none of the patients who underwent complete removal of the CP died postoperatively. This observation is another argument supporting the surgical strategy of aiming for complete tumor removal.

A limitation of our study is the retrospective study design. Another limitation is the relatively few cases, which is a well-known dilemma in single-center series reporting on rare diseases like CP. Our series is already among the larger series that specifically address adult CP. We hope that prospective and multicenter studies will solve this problem in the future. Notably, the prospective German Craniopharyngioma Registry for Adults has been launched to solve some of the unsettled issues in adult CP.

To sum up, our study demonstrated no significant differences in the success rates of complete resection, recurrence-free survival, or postoperative complications between primary and repeat surgery for CP. Therefore, we cannot confirm the inferior outcome for repeat surgery that has been described in the literature. Thus, reoperation, possibly with an attempt at complete resection, should be included in therapeutic considerations for patients with CP recurrence. However, we emphasize that inappropriate surgical risks should be avoided.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

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