German Society of Pediatric Oncology and Hematology (GPOH)
Association of Pediatric Endocrinology (APE),
German Society of Endocrinology (DGE)
Working Group Pediatric Radiation Oncology (APRO) -
Task force of the German Society of Radiation Oncology (DEGRO)

KRANIOPHARYNGEOM 2007

Multicenter Prospective Study
of Children and Adolescents with Craniopharyngioma

Study Protocol
01 Oct. 2007 edition
Certified by the German Cancer Society (Seal of Approval A)

In collaboration with:
German Society of Neuropediatrics (GNP)
Neurooncology German task force (NOA)
German Society of Neuroradiology (DGNR)
German Society of Neurosurgery (DGNC)
German Ophthalmology Society (DOG)
German Society of Neuropsychology (GNP)
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This current multicenter study of children and adolescents with craniopharyngioma applies a multi-discipline approach encompassing diagnostics, therapies and follow-up care associated with neuropsychiatrics, pediatric oncology, neuroradiology, neurosurgery, radiation therapy, and pediatric endocrinology. Due to the rarity of the disease, standardized data capture was established within the framework of the International Society of Pediatric Oncology (SIOP) – helped by evaluation forms that also are used for patients from Austria, Switzerland, Benelux, Scandinavia, France, Great Britain, Italy and Spain. By increasing the international cooperative case numbers, this international standardization of data improves the SIOP joint data analyses effort with respect to diagnostics, therapy and prognosis of children and adolescents with craniopharyngioma.

KRANIOPHARYNGEOM 2007 is open to other collaborative studies in its pursuit of multicenter, interdisciplinary participation and cooperation. Material and data will be made available to KRANIOPHARYNGEOM 2007 colleagues with approval of the study commission.

This study protocol was compiled with great care. Nevertheless, errors cannot be completely excluded. It is therefore particularly important to emphasize that each treating physician is solely responsible for any therapy rendered. The study directorship accepts no legal responsibility for possible consequences resulting from use of this study protocol.

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According to the joint German federal committee (G-BA) resolution of 16 May 2006, a legal directive was passed effective 01 January 2007 stipulating that pediatric patients with oncological diseases are to be treated exclusively in institutional pediatric oncology centers and recruited in therapy optimization studies the German Society of Pediatric Oncology and Hematology (GPOH). Children and adolescents with craniopharyngioma were specifically included in this legal directive. The outpatient care of children and adolescents with craniopharyngioma under follow-up care are not specifically affected by this G-BA decision. Because a multidisciplinary approach is necessary to not only to diagnose and treat craniopharyngioma but also to provide optimal follow-up care for these patients, the KRANIOPHARYNGEOM 2007 study commission requests that all colleagues and specialists involved in the follow-up care of craniopharyngioma patients fully participate by registering all patients.

Patient agreement to be registered in this study (pp. 95, 102, 103) and permission of transmission and processing of their data (p. 104) should be obtained early from parents and patients – either pre- or postoperatively. Agreement to randomization (pp. 97, 100) should be obtained as a second step after radiological assessment regarding the degree of resection has been received, and/or fulfilment of all inclusion criteria (p. 37).
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Craniohypophyseal tumors are rare, dysontogenetic sellar masses. A German retrospective cross-sectional craniohypophyseal study (HIT-ENDO) examined 306 children and adolescents with craniohypophyseal tumors regarding their prognoses. Even though a high overall survival rate of 92% was found, the quality of life and functional capacity of the long-term surviving patients were compromised due to hypothalamic involvement of craniohypophyseal tumors. Hypothalamic involvement was associated with eating disorders, pronounced obesity, a high rate of neurosurgical operations and late-effects/morbidities. The retrospective analysis found no long-term influence on patients’ quality of life from radiation treatment. The retrospective nature of data evaluation in HIT-ENDO in regard to neuroradiological assessment of tumor localization and determination of hypothalamic involvement was difficult.

The multicenter prospective surveillance study KRANIOPHARYNGEOM 2000 evaluated the data of 120 children and adolescents with newly diagnosed craniohypophyseal tumors regarding their neuroradiological diagnostics, therapy and prognosis (quality of life and functional capacity). Data on imaging, histology and QoL were assessed and tested by reference centers. Therapy recommendations and randomization were not included in the scope of KRANIOPHARYNGEOM 2000. The intermediate results of the KRANIOPHARYNGEOM 2000 (interim analysis as of October 2008) were as follows:

• The expected 120 patient case number in 5 years was reached and the data attained show a high degree of data completeness (80%).
• Hypothalamic involvement in a craniohypophyseal tumor represents the most important risk factor for a restricted long-term prognosis (quality of life and functional capacity).
• A radical excision is not recommended in cases of hypothalamic involvement with consideration of the after-effects from such a procedure.
• A complete resection of the craniohypophyseal tumor succeeds in ca. 50% of cases (relapse-free survival rate three years after complete resection (n=47): (EFS 0.63 ± 0.09).
• The low event-free survival rate three years after incomplete resection (n=66) (EFS: 0.33 ± 0.07) verifies the high rate of progression of residual tumor after incomplete resection.
• Biological risk factors of residual tumor progression are not yet known or investigated.
• No prospective studies on the appropriate time point of irradiation following incomplete craniohypophyseal tumor resection have yet been published. Retrospective investigations and reports yield an inconsistent outlook.

In light of the poor long-term prognosis of patients with hypothalamic-involvement of craniohypophyseal tumors, the controversy continues regarding optimal timing of irradiation after incomplete resection. Advocates of radiation therapy in concert with primary surgery point out that, based on an imminent progression, further surgical intervention could be pre-emptively avoided with immediate irradiation and with that, an increased risk to the long-term prognosis could be avoided as well. On the other hand, irradiation upon detection of tumor progression has the advantage of selectively irradiating only the progression and thereby sparing patients without residual tumor progression the irradiation in the first place. Potential disadvantages of non-immediate irradiation of residual tumor include the necessity to irradiate a progressive mass. Based on missing data in the literature, this scientific and clinical controversy is not yet settled.

Therefore, KRANIOPHARYNGEOM 2007 will scrutinize, by means of a randomized investigation of craniohypophyseal tumor patients aged ≥5 years at the time of incomplete resection, this question of the hour: the optimal timing of postoperative irradiation of residual tumor (immediate postoperative XRT vs. XRT at the time of progression). The primary goal of KRANIOPHARYNGEOM 2007 is the patients' quality of life assessment (PEDQOL questionnaire) three years after the stratified randomization. Closely-related subgoals are examinations of progression-free and overall survival rates. For all other patients (after complete resection as well as for those patients under 5 years of age regardless of the degree of resection) postoperative data will be evaluated in a surveillance study (KRANIOPHARYNGEOM 2007).
Collaborative investigations will examine molecular genetic risk factors regarding biological growth behaviour of craniopharyngioma and progression of residual tumor remnants.

Because of the rarity of the disease, the International Society of Pediatric Oncology (SIOP) succeeded in obtaining a uniform evaluation consensus on data regarding brain tumor groups. This joint European SIOP registration databank of children and adolescents with craniopharyngioma is a component of the study protocol. Based on this international cooperation and standardization of data collection and definitions of parameters, it is hoped that important questions can thereby be answered in the future and that a larger, more homogeneous patient cohort can be evaluated.

This study aspires to innovative research approaches:

1. **KRANIOPHARYNGEOM 2007** is the first randomized study in children and adolescents with craniopharyngioma.

2. As a main goal **KRANIOPHARYNGEOM 2007** analyzes for the first time children and adolescents with a brain tumor for postoperative changes in quality of life.

3. **KRANIOPHARYNGEOM 2007** data evaluation is based on an internationally-coordinated databank. A goal of this cooperative elevation within the context of SIOP is to increase the patient cohort size for future analyses.

The duration of the study is subdivided into a phase running up until the interim analysis (IA), and the recruitment phase following IA – running up until the end analysis (EA). The IA is carried out after recruitment of 20 randomized patients and a follow-up observation for three years. Based on the recruitment numbers of the precursor study, the **Interim Analysis (IA)** will begin probably around 5.5 years after study initiation (duration of IA data analysis is ca. ½ year).

After appr. 6 years study duration, the following scenarios are possible:

- If the IA (interim analysis) indicates an early therapy effect (i.e. 5.5 years after study initiation), recruitment will be discontinued at the time of IA. EA begins appr. 7 years after study initiation; EA duration: ½ year. In this scenario, **study endpoint would be appr. 7.5 years after study initiation**.
- If the IA yields little or no therapy-effecting results, the study would be stopped at IA. In this scenario, earliest **study endpoint would be appr. 6 years after study initiation**.
- If the IA yields a moderate therapy effect, the recruitment period would be extended following IA somewhere around 4 years to a maximum of 6.5 years. Total recruitment duration from year-0 to year-10 would be extended to a maximum of 12.5 years. A follow-up period of 3 years would then ensue. In this scenario, **study endpoint would be appr. 13 years with a maximum of 15.5 years after study initiation**.

Considering the lengthy period of this study, changes and advancements in surgical and/or radiooncological therapeutic treatment can not be ruled out as having an effect on the EA (end analysis), knowing that any advancements in either of these areas would affect both therapy areas equally with respect to treatment modalities within the context of randomization.
Preoperative imaging (MRI, native + enhancement; CT native) → surgery → postoperative imaging (MRI, native + enhancement; CT native if necessary)

Reference radiological evaluation of pre- and postoperative MRI / CT assessment of the degree of resection (complete versus incomplete)

Complete Resection
- All Patients, any age
- Continuous observation in KRANIOPHARYNGEOM Surveillance Study

Incomplete Resection
- Patients < 5 years of age
- Continuous observation in KRANIOPHARYNGEOM Surveillance Study
- Patients ≥ 5 years of age
- Quality of Life (PEDQOL) neuropsycholog. testing 3rd mth (60–90 days) post-op

Stratified randomization 3 months post-op for all patients ≥ 5 years of age with incomplete resection

Treatment arm I
- Planning of localized XRT immediately following surgery (after randomization)
- Reference assessment of XRT plans
- Subsequent execution of XRT
- MRI monitoring post XRT

Treatment arm II
- MRI monitoring in 3 month intervals with MRI reference assessments of progress
- At sign of progression (>25%): localized XRT, (if needed after subsequent surgery) and reference assessment of XRT plans
- MRI monitoring post XRT
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1. Introduction

Craniopharyngiomas are rare, dysontogenetic midline tumors, actually embryogenic malformations from ectoblastic remnants of Rathke's pouch. They are usually cystic, occasionally solid, sometime mixed (solid/cystic) and are non-malignant. The adamantinous craniopharyngiomas predominate in children and adolescents, the squamous papillary histological variant in adults, and mixed have been known to occur in both groups. Half of all suprasellar tumors are craniopharyngiomas and can be either supra- and/or intrasellar localized. Patients are typically identified by neurological and/or brain pressure symptoms and are frequently diagnosed via endocrinological disorders (growth hormone deficiency, central diabetes insipidus, hypogonadism, obesity) and/or by the ophthalmological disorder bitemporal hemianopsia. Typical imaging leads to the suspected diagnosis of craniopharyngioma. The diagnosis is confirmed by histological assessment of tumor tissue.

It is the task of an experienced, multidisciplinary team of neurosurgeons, neuroradiologists and radiotherapists to decide the appropriate treatment strategy regarding surgical approach and intraoperative attainable degree of resection (primary intentions being complete resection, incomplete resection, biopsy, cyst decompression, irradiation therapy).

An individual-oriented treatment process is highly justifiable as prognosis is based on adverse late effects. Endocrine deficiencies, hormonal substitution therapy, extreme obesity from hypothalamic-related eating disorders, visual impairment, and neurological and neuropsychiatric disturbances can affect postoperative health status and therefore craniopharyngioma patients’ quality of life (Gutjahr 1999).

Prospective, randomized investigations of influencing factors associated with the various therapeutic strategies regarding craniopharyngioma patients’ prognoses do not yet exist due to the rarity of the disease. It is for this reason that the debate has yet to be settled between proponents of primary radical surgical strategy and advocates of a biopsy accompanied by follow-up radiation therapy.

The present investigation is a prospective, multicenter study evaluating craniopharyngioma patients’ prognoses following defined therapeutic strategies. A stratified randomization of two treatment arms will be conducted with respect to timing of postoperative irradiation (immediate XRT versus XRT at the time of progression) for the subgroup of patients ≥5 years of age at the time of incomplete resection. The stratification criterion is based on the baseline QoL assessed 60-90 days after incomplete resection. QoL as measured by PEDQOL (a pediatric quality of life instrument) domain "physical function": ≤ 56 vs. > 56 will serve as a stratification criterion. We will investigate whether an immediate, postoperative irradiation is superior to progression-contingent irradiation based on alterations to quality of life (PEDQOL) from the time of randomization (3rd month after surgery/diagnosis) to 3 years after randomization. Progression-free survival and overall survival will be examined as closely-related subgoals.

Data evaluation and definitions of parameters are standardized based on a consensus of the SIOP brain tumor subgroup on childhood craniopharyngioma. International standardizations of data capture with respect to diagnostics, therapy, and prognosis of childhood craniopharyngioma have been put in place to increase international cooperative case numbers and thereby facilitate the success of joint SIOP data analyses. Further goals of the study are to establish quality standards and compare the various therapeutic strategies with respect to their effectiveness and impact on the quality of life of treated patients. Recommendations for therapeutical strategies shall be compiled based on the results of these KRANIOPHARYNGEOM 2007 investigations.
2. Background

2.1 Embryology
It was Swiss physiologist Albrecht von Haller who in 1766 first reported an intracranial gland located in the bone niche at the anterior skull base area with clearly circumscribed front and rear parts, later named the "hypophysis cerebri" (pituitary gland) by German physician and anatomist Samuel Thomas von Sömmering in 1778. Seven years later, Mihalkovics postulated that an ectodermal diverticulum of the stomodeum constituted the embryonic precursor structure of what would develop into the pituitary gland, an observation confirmed by German embryologist Martin Heinrich Rathke in 1938, explaining why the craniopharyngeal duct has since has been known as Rathke’s pouch.
Most craniopharyngiomas emerge from the ectoblastic remnants of the above described Rathke’s pouch and occur anywhere along this anatomical localization. Another hypothesis suggests that some craniopharyngiomas develop from the cell rests of the residual metaplasia into desquamated epithelial – remnants of the stomadeum section that contribute to the development of the buccal mucosa (Carmel 1989; Miller 1994).

2.2 Pathology
Adamantinous craniopharyngiomas are the predominant type occurring in children and adolescents and are usually cystic in formation. Squamous papillary craniopharyngiomas occur more frequently in adults, are usually solid rather than cystic, and rarely develop calcifications. Mixed types (solid/cystic) are also known to occur. The contents of the adamantinous craniopharyngioma cysts consist of a cholesterol-rich, brownish-yellow oily fluid with partially firm components. The squamous papillary cyst fluid is less oily (Weiner 1994; Miller 1994).
Craniopharyngioma tumors develop slowly (proliferation index <1%). The adjacent healthy brain tissue frequently reacts with the formation of a dense, fibrillary gliosis consisting of Rosenthal fibers that macroscopically appear to be pseudopapillae. In spite of the surrounding gliosis, the adamantinomatous craniopharyngiomas in particular display multiple tumors invasions into the adjacent brain tissue. Controlling for the degree of resection, the two histological variants (adamantinomatous vs. squamous papillary) demonstrate no differences in recurrence rates (Weiner 1994; Miller 1994).
Immunohistological chemical characterizations of adamantinomatous types reveal especially high molecular keratine, which appears to be is lower in squamous papillary types. The significance of expressions of P-glycoprotein, somatostatin, and estrogen receptors is unclear.
Various chromosomal peculiarities (chromosomes 2 and 12) in the craniopharyngioma tissue have been found in some individual cases. It is important to note that no genetic predisposition for craniopharyngioma has yet been established.
A diagnostic differentiation of xanthogranuloma (cholesterol granuloma) occurring in the sellar region should be highlighted. The histology of xanthogranuloma includes cholesterol crystals, macrophages, chronic sellar inflammation, necrotic debris and hemosiderin deposits – a histological profile derived from an investigation of a degenerative adamantinomatous craniopharyngioma. More recent pathological investigations reveal that xanthogranuloma is a histological discrete, sellar-region entity occurring especially in adolescents and young adults. Its more favourable prognosis is a consequence of the intra-sellar tumor localization, smaller volume and superior surgical resectability. Non-adamantinomatous epithelium tubular structures are histological localized, whereas adamantinomatous epitheliums are typically absent of xanthogranuloma and found in less than 10% of cases.

2.3 Epidemiology
Craniopharyngioma is the most common non-glial intracranial tumor in the pediatric population with an incidence rate of 0.5–2 per million people per year, 30 to 50% cases of whom are children and adolescents. Craniopharyngiomas constitute 1.2 to 4% of all pediatric intracranial tumors. The incidence rate is concentrated among two age groups with peaks in children 5 to 10 years of age and adults 50 to 75 (Sanford 1991). Craniopharyngiomas are systematically recorded by the German Pediatric Cancer Registry in accordance with international guidelines (Kramorava 1996). Even so, as is generally the case with non-chemotherapy treated brain tumors and especially with craniopharyngiomas, the total degree of recruitment has not yet reached a satisfactory point whereby
a valid rate of incidence can be calculated. KRANIOPHARYNGEOM 2007 is predicted to markedly improve the rate of epidemiological craniopharyngioma registration. Between 1980 and 2001, 385 craniopharyngioma patients under the age of 18 were identified and registered. Of that total, 345 diagnosed patients were under 15 years of age. The median age at the time of diagnosis was 8.6 years in this under-15-years-of-age patient group (sex ratio 1:1). Their overall survival rate was 93% after 3 years of observation, 91% after 5 years, and 87% after 10 years of observation. Patients who became ill and were treated in the 1980s had a lower survival rate probability (p<0.05) than patients who were diagnosed in the 1990s (5-year survival rate probability: 88% vs. 96% respectively) (H.L. Müller 2001) reflecting probably advanced technical possibilities in diagnostics and treatment.

2.4 Anatomical localization
The most frequent localization is suprasellar with an intrasellar component as well. Around 20% of craniopharyngiomas are exclusively suprasellar and approximately 5% are exclusively intrasellar (Harwood Nash 1994). A tumor invasion into the anterior cranial fossa is found in 30% of cases, while 23% expand into the middle cranial fossa. Rare, ectopic localizations occur at the sphenoid bone, pharynx and cerebellopontine angle (niche between the brainstem and cerebellum). Papillary-type craniopharyngioma invasion is often found in the third ventricle (Weiner 1994). In 20% of the cases with retroclival expansion, expansions were co-caused by solid tumor components.

2.5 Clinical symptoms
The clinical manifestation at the time of primary diagnosis is dominated by multiple non-specific signs and symptoms of increased intracranial hypertension such as headaches and morning dry heaves. Additional craniopharyngioma symptoms include impaired vision (in 62–84% of cases, more commonly in adults than children), endocrine deficits (in 52–87% of cases, more frequent in children and associated mostly with squamous papillary craniopharyngiomas). Endocrine deficits affect the hypothalamic-pituitary axis regulating growth hormone (75%), gonadotropins (40%), adrenocorticotropic hormone (ACTH) (25%), and thyroid-stimulating hormone (TSH) (25%). Central diabetes insipidus exists preoperatively in 17% of craniopharyngioma-diagnosed children and 30% of diagnosed adults (Sklar 1994).

Medical records of 311 craniopharyngioma patients were analyzed in the retrospective HIT-ENDO study regarding their primary manifestation profiles and case history durations. Initial symptoms and respective case-history durations until diagnosis included headaches (52%; median case-history duration 24 months [range: 0.5–96]), impaired vision (18%; 6 months [1–48]), reduced growth rate (15%; 33 months [12–96]), daytime sleepiness (8%; 2 months [0.1–6]), polyuria/polydypsia from diabetes insipidus (5%; 26 months [12–48]) and weight gain (5%; 24 months [24–48]). The total case history duration of the 311 patients averaged around 12 months (range: 0.5–96 months). A data analysis on growth before diagnosis of craniopharyngioma was performed, revealing that restricted growth rates could be detected as early as 10–12 months of age (H.L. Müller 2004). The correlation between case history duration and patient functional capacities using the German-developed functional abilities assessment questionnaire [FMH] taken by patients at their latest follow-up visit did not reach statistical significance.

The combination of major symptoms – headache, impaired vision, growth impairment and polyuria/polydypsia – should arouse suspicion of a craniopharyngioma.

2.6 Imaging diagnostics
Both computerized tomography (CT) and magnetic resonance imaging (MRI) show craniopharyngiomas to be cystic tumors occurring mostly in the suprasellar and/or intrasellar region. CT can better detect calcifications, which exist in almost 100% of the tumors. MRI reveals that craniopharyngiomas have highly variable signal intensity depending on the protein content of the cysts. The cysts appear hyperintense, most frequently in T1- and T2-weighted images. Solid tumor components and cyst membranes appear isointense in T1-images, often with a mildly heterogeneous structure. Cyst contents appear hyperintense in T1-weighted images when high in protein or blood product. Gadolinium enhancement reveals a ring shape enhancement of the cystic capsules and mostly inhomogenous, intensely enhanced solid tumor components (Harwood Nash 1994). The most common localization is a suprasellar mass with a smaller intrasellar component. Around 20% of
craniopharyngiomas are exclusively suprasellar localized and 5% are exclusively intrasellar localized. Neuroimaging reveals that squamous papillary craniopharyngiomas lack the calcification and homogenous structural features common to the classic adamantinomatous variant (Crotty 1995; Miller 1994). The combination of solid, cystic and calcified tumor components is a radiological diagnostic clue that differentiates craniopharyngiomas from other rare, sellar region tumors such as Rathke cleft cysts, necrotizing pituitary gland tumors, aneurysms, gliomas, colloid cysts and granulosa cell tumors. Assessing discernibility of the pituitary gland is the key to distinguishing craniopharyngiomas from cystic degenerated pituitary tumors. A discernable pituitary always argues against a pituitary adenoma (Warmuth-Metz 2004).

<table>
<thead>
<tr>
<th>Differential Diagnoses in Craniopharyngioma Imaging</th>
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<tr>
<td>pituitary adenomas</td>
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<td>hypothalamus and optical tract gliomas</td>
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<td>Rathke cleft cysts</td>
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<td>epidermoid tumors</td>
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<td>arachnoid cysts</td>
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<td>inflammatory variations</td>
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2.7 Natural course of disease
Craniopharyngiomas histologically consist of differentiated tissue of low-grade malignancy. All WHO-graded brain tumors occurring in children are assessed as “of malignant type” with an individual degree of malignancy. This especially applies to “low-grade malignant” craniopharyngiomas because the clinical course of this tumor type is characterized by its capacity to infiltrate surrounding normal tissue due to its localization near the hypothalamic-pituitary axis structures as well as the optic nerve and chiasm. The prognosis is unfavourable without therapy.

2.8. Treatment strategies

2.8.1 Patient care strategies for hydrocephalus
Tumor-related disturbance of cerebrospinal fluid (CSF) often preoperatively causes hydrocephalus of varying severity. This intracranial pressure can often be relieved with preoperative dexamethasone therapy. Perioperative dexamethasone therapy induces prophylaxis of brain oedema as well as hormone substitution due to the likelihood of postoperative low cortisol levels. Preoperative implantation of permanent CSF-draining shunts remains controversial and poorer prognoses of patients having undergone said treatment have been reported (Goel 1995). Tumor resection is the preferred treatment for restoring normal CSF flow.

2.8.2 Cyst aspiration
Implanting an intracystic catheter with a subcutaneous reservoir makes it possible to reduce the cyst volume and prolong the interval before radiotherapy or surgical resection in small children. In particular for patients with large, mass-exerting cysts and consequential severely limited vision, a two-staged strategy has been discussed: first stage being cyst drainage to relieve pressure and improve vision; second stage being tumor resection (Pierre-Kahn 1994). The authors emphasize that this two-stage strategy and especially the surgical cyst drainage reduces a considerable risk to the patient’s vision.
2.8.3 Surgical access approach
The surgical approach is fundamentally determined by the localization and dimension of the craniopharyngioma. The standard approach is a right frontotemporal craniotomy, enabling a good anatomical overview of the sellar and perisellar structures. Purely intrasellar localized craniopharyngiomas can be successfully resected via a transsphenoidal approach. Small and especially cystic tumors are also best resected using this approach (Einhaus 1999). Fahlbusch et al. report a lower incidence of endocrine deficiency after craniopharyngioma resection via the transcranial approach (Fahlbusch 1999).

Post operative CSF rhinorhea occurs in 13% of transsphenoidal approach resections (Laws 1994) and usually ceases with pressure relief via lumbal plexus CSF drainage. CSF rhinorhea occurs in 4% of resections independent of the surgical approach if the tuberculum sellae has also been resected (Hoffman 1992).

2.8.4 Surgical techniques
Surgical procedure progresses step-by-step with alternating decompression and excision along a usually pseudcapsular marked boundary zone. Special caution is given to contact with adjacent vessels (carotid artery, cerebellar artery, anterior cerebral artery), the optic nerve and chiasm, and the hypothalamus. Modern surgical resources such as lasers and ultrasonic surgical aspirators often push the boundaries of craniopharyngioma resections, enabling the surgeon, under optimal visibility possible, to remove tumor material step by step using microsurgical instruments.

Surgical strategy is disputed in the literature with respect to intended resection grades (limited vs. radical). Planned radical resection is critically viewed by many authors due to the surgically induced deficits, especially hypothalamic, and the high relapse rate (10–20%) despite complete resection (Rajan 1993).

Scarring resulting from irradiation after incomplete resections worsens the reoperation outcome in cases of relapses compared to a reoperation after primary resection without radiation therapy. No prospective studies on patients’ prognosis in regard to therapy selection criteria have yet been published, making them urgently necessary in light of the above described controversy. That said, based on the results of the KRANIOPHARYNGEOM 2000 study and HIT-ENDO, radical surgical action is most emphatically dissuaded in cases of craniopharyngioma with hypothalamic involvement.

2.8.5 Intended complete resection
Surgery is the central focus of primary therapy management, the wait-and-see strategy being the worldwide accepted standard following complete resection (Thompson 2005). However, the radical surgical intervention is frequently accompanied by unjustifiable consequences, meaning less aggressive surgical action is often chosen, leaving residual postoperative tumor tissue behind. Incomplete resection frequently leads to an early recurrence. Given this therapeutic state of affairs, postoperative irradiation is often performed.

The therapy of first choice for favourably localized tumors is an attempted microsurgical complete resection while protecting the functional integrity of adjacent brain tissue. This therapeutic approach is controversial for unfavourable localized tumors, some arguing that planned limited resection (biopsy, incomplete resection) plus immediate irradiation should be performed instead. The final decision regarding the possibility of a complete resection is best made intraoperatively by the surgeon.

2.8.6 Planned limited resection (biopsy, incomplete resection)
A literature survey shows that incomplete tumor resection followed by immediate radiation therapy achieves local tumor control in 80% of cases, the 10-year survival rate being 77%. Three authors reported a survival rate of 66% after a 20-year observation (Becker 1999). In the largest series, Rajan and colleagues (1993) reported that, out of 173 craniopharyngioma patients (77 of which were children under 16 years of age), 83% experienced an event-free survival rate after 10 years and 79% after 20 years. These results are comparable with statements in the literature regarding local tumor controls, recurrence-free survival rates and survival rates of total-resected craniopharyngioma patients (Becker 1999; Rajan 1993; Fahlbusch 1999). Prospective, multicenter investigations of long-term consequences and patient quality of life (QoL) after limited resection plus immediate irradiation compared to those having undergone planned complete resections have yet to be published.
2.8.7 Controversy: complete versus incomplete resection + irradiation

The above mentioned debate regarding craniopharyngioma treatment strategies for children and adolescents is acute and remains unsettled. Following incomplete resection, tumor progression is sustained in 71% of patients. Recurrence rate after microsurgical complete resection is 0–20%; progression rate after incomplete resection plus immediate irradiation is 21% (Einhaus 1999; Becker 1999).

These results suggest that there is no significant statistical difference between the two therapeutic strategies regarding postoperative tumor control. Nonetheless, long-term consequences and QoL of treated patients need to be factored into the debate. No prospective, multicenter investigations have yet been published.

A follow-up study of 139 children with craniopharyngioma who had undergone microsurgical complete resections yielded that patient QoL significantly depended upon the experience of the operating neurosurgeon. If the neurosurgeon had performed two or more craniopharyngioma resections per year, 87% of their patients had a postoperative QoL rating of good. If the surgeon had performed less than two craniopharyngioma resections per year, only 52% rated QoL as good. QoL was classified as good for 83% of patients having undergone incomplete resections following by immediate irradiation (Sandford 1994).

Endocrine substitution was necessary 95% of the time for patients with incomplete resections and 94% of the time for patients with incomplete resections plus immediate irradiation treatment (Becker 1999). Statistical analysis indicated that completely resected patients required hormonal substitution soon after surgery, whereas hormonal deficits in incompletely resected and irradiated patients developed later on (Einhaus 1999). Differences are reported regarding complications involving vessels adjacent to the craniopharyngioma, with an 8% occurrence after complete resection versus 1–2% for cases after limited resection combined with irradiation. Visual impairment was estimated in up to 20% after complete resection versus 10% after incomplete resection + irradiation. Complications of infection and postoperative sequelae such as seizures occurred more often in complete resections than in limited resections. Deteriorations in cognitive functional capacities have been reported for complete resections cases with hypothalamic involvement. Reports in the literature indicate a lower probability (6–15%) in patients after limited resection plus irradiation. Radionecrosis is described in a few, very isolated cases.

2.8.8 Therapy strategies after incomplete resection

In one investigation (Hoffman 1992), a complete resection case rate of 90% was assessed following microscopic surgical inspection. The 28.9% relapse rate in this cohort points out that the actual resection grade based on intraoperative inspection is not always reliable.

Therapy strategies following incomplete resection continue to be debated. The HIT-ENDO retrospective multicenter cross-sectional study examined 306 children and adolescents with craniopharyngioma with respect to their therapy strategy and long-term prognosis. Overall survival rates for irradiated patients were 94±4% vs. 93±5% for non-irradiated patients. The prospective, multicenter surveillance study KRAINIOPHARYNGEOM 2000 examined recurrence rates after complete resection and the craniopharyngioma progression rates after incomplete resection as well as the influence of irradiation (XRT) regarding frequency and timing of tumor relapses and progressions in 101 craniopharyngioma patients. These 101 craniopharyngioma patients were recruited and prospectively examined from 2001 to March 2006. Median age at diagnosis was 9.4 years (1–17 years of age). Data regarding neurosurgical and irradiation procedures were prospectively captured with a high degree of completeness (80–90%). Twenty-four (24) of the 101 craniopharyngioma patients had irradiation therapy at a median age of 11.5 years (4–18 years of age) after complete or incomplete resection – 10 months on average after their craniopharyngioma diagnosis. All 24 of these patients had planned 3D computerized tomography (CT) radiation therapy. The average total dose was 52.5 Gray (50.4–60 Gy). An interim analysis of event-free survival time (EFS after 3 years) yielded high rates of early occurrences for tumor progressions after incomplete resection (EFS: 0.22±0.09) and relapses after complete resection (EFS: 0.60±0.10). Tumor progressions were found during the observation period following irradiation (EFS: 0.57±0.15) in 6 of the 23 evaluable irradiated patients (25%).
We conclude that both craniopharyngioma relapses after complete resection and tumor progressions after incomplete resections appear to occur frequently, even after radiation therapy during the first 3 years after diagnosis. Therefore, regular monitoring of imaging and clinical status is recommended, especially in the first years following craniopharyngioma diagnosis in children and adolescents. The question regarding ideal timing for radiation therapy following incomplete resection carries exceptional significance in light of the high rate of tumor progression after incomplete resection. As a result of our earlier prospective evaluation (KRANIOPHARYGEOM 2000), randomization of radiation therapy timing following incomplete craniopharyngioma resection will be performed in KRANIOPHARYGEOM 2007.

No prospective studies as to what extent the timing of radiation therapy initiation on residual tumor influences long-term prognosis have yet been published. Moon et al. (2005) retrospectively examined the question as to what extent early postoperative radiation therapy of non-resected tumor influences the progression-free survival probability and QoL of incomplete resected patients in 50 patients from a university center collective. The investigated parameters regarding QoL were restricted in this study to ophthalmologic results and pharmaceutical osmolality regulation using DDAVP. Overall survival rates and probability of progression-free survival, as well as the ophthalmologic and diabetes insipidus regulation results, were statistically independent from the postoperative irradiation timing.

2.8.9 Treatment strategies in cases of tumor relapse or progression

Overall survival rate was 77% and progression-free rate was 72% in a series of 25 patients with recurring craniopharyngioma treated at the Royal Marsden Hospital. The degree of resection in relapse surgery had no statistical effect on long-term prognoses. The results after irradiation treatment of relapses were comparable to surgery with postoperative irradiation treatment at the time of primary diagnosis (Jose 1992).

Patients at Chicago Children’s Memorial Hospital with recurring craniopharyngioma reported second relapse-free rates of 67% (2 years) and 0% (5 years) respectively following one surgical treatment of the relapse. Following irradiation of craniopharyngioma relapses, relapse-free rates were 100% (5 years) and 83% (10 years) respectively. Surgical treatment of relapses had a higher complication rate (Kalapurakal 2000).

Twenty-nine relapse patients at Columbia Presbyterian Hospital reported relapse-free rates following one surgical treatment of 29% (5 years) and 18% (10 years), respectively. Ten patients receiving surgical treatment combined with irradiation reported relapse-free rates of 71% (5 years) that remained 71% after 10 years. Morbidity and mortality rates were increased in the group of only surgically-treated relapse patients. Three patients died within the first 4 weeks following surgery (Sung 1981).

Tumor control rates following surgery combined with irradiation was 80% in a craniopharyngioma patient series with recurring disease at the University of Pennsylvania (Weiss 1989). A clearly delineated prognosis for relapse patients was found in the Thomas Jefferson Hospital patient series: 20-year overall survival rates were 25% for relapse patients; 78% for patients without relapses (Regine 1992). In light of these statistics and the clearly superior progression-free rate of relapses treated with immediate irradiation therapy, the combination of surgical treatment plus immediate irradiation is recommended for relapse cases.
2.9 Irradiation

Position and rational regarding irradiation
In clinical practice, the value of postoperative residual tumor irradiation is both unclear and inconsistently regarded. Some favour immediate postoperative irradiation in the event of life-impairing clinical conditions, proactively preventing tumor progression (Thompson 2005). On the other hand, some favour a wait-and-see procedure, delaying irradiation in order to reduce both its necessity and the negative consequences associated with radiation therapy. Inarguably, immediate postoperative irradiation significantly delays tumor progression (Stripp 2004). However, progression-contingent irradiation appears to be highly effective as overall survival is statistically unaffected by this wait-and-see strategy (Stripp 2004). Three recent series retrospectively compared the immediate postoperative irradiation strategy with progression-contingent deployment (Stripp 2004; Tomita 2005 and Moon 2005 – see table below).

No statistical difference could be assessed with respect to the overall survival. No difference in progression-free survival was detected between immediate irradiation and progression-contingent treatment in the series conducted by Moon. However, progression-contingent irradiation was clearly associated with a higher negative affect on QoL, which is why the authors favoured immediate irradiation (Moon 2005). Investigated QoL parameters were restricted in this study to ophthalmologic results as well as data regarding pharmaceutical osmolality regulation using DDAVP. Overall survival rates and the probability of progression-free survival, as well as the ophthalmologic and diabetes insipidus regulation results, were statistically independent from postoperative irradiation timing.

Relapse-free overall survival rates were 83% and 70% after 5 and 10 years respectively in the series conducted by Tomita. The corresponding numbers for patients after incomplete resection followed by immediate irradiation were 71% and 36% after 5 and 10 years respectively. After incomplete resection without radiation therapy, the relapse-free survival rate after 5 years was merely 9% (statistically extremely inferior to immediate irradiation). Progression-contingent irradiation achieved nearly identical final overall survival- and progression-free survival rates of 90% and 70% respectively, meaning progression-contingent irradiation in this series was highly effective.

Table: immediate vs. delayed irradiation / craniopharyngioma survival rate ratios

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Cohort size</th>
<th>Immediate irradiation</th>
<th>XRT at progression</th>
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<tbody>
<tr>
<td>Sung et al.</td>
<td>1982</td>
<td>10</td>
<td>—</td>
<td>70.9% 10 y OS</td>
</tr>
<tr>
<td>Regine et al.</td>
<td>1992</td>
<td>19</td>
<td>78% 20 y OS</td>
<td>25% 20 y OS</td>
</tr>
<tr>
<td>Stripp et al.</td>
<td>2004</td>
<td>40</td>
<td>83% 10 y OS</td>
<td>86% 10 y OS</td>
</tr>
<tr>
<td>Tomita et al.</td>
<td>2005</td>
<td>30</td>
<td>71% 5 y PFS</td>
<td>90% 5 y PFS</td>
</tr>
<tr>
<td>Moon et al.</td>
<td>2005</td>
<td>50</td>
<td>91.3% 10 y PFS</td>
<td>91.2% 10 y PFS</td>
</tr>
</tbody>
</table>

OS: Overall survival
PFS: progression-free survival
Therapy results
Therapeutic consequences of irradiation and surgery remain controversial. Above all, the influence of treatment sequence (immediate irradiation vs. progression-contingent irradiation of residual tumor) on QoL is unclear in the retrospective data published to date. The retrospective analysis conducted by Merchant (2002) sited primary therapy FSIQ (full scale IQ) losses of 9.8 points after a single complete resection compared to a loss of 1.25 points after limited resection followed by irradiation. For a repeat surgical intervention carried out following a relapse, the loss was 13.1 points, statistically suggesting that radical and/or repeated surgeries seem to generate rather negative influences on neurocognitive functions compared to limited surgical intervention plus immediate radiation treatment. Irradiation is very frequently associated with hypothalamic-pituitary function deficits. The fact of the matter is that only very limited available retrospective data exists. In the series from the Royal Marsden Hospital (Rajan 1993), all axes were affected following irradiation. Deficits at the time of diagnosis were between 7.3 and 18% compared to those following irradiation of between 25.3 and 66%. Complete resections were renounced in this series. Complete resections have been linked to panhypopituitarism in 80−100% of cases. Merchant et al. investigated growth hormone levels following irradiation with regards to treatment timing and extent, evaluating the integral dose distribution in the hypothalamus. A growth hormone deficiency adjusted itself in 11 of 25 children after 6 months and in 20 of the 25 children after 12 months. The probability of occurrence depended upon the integral dose distribution (Merchant 2002).
KRANIOPHARYNGEOM 2007 will evaluate dose-volume histograms, prospectively generating an integral dose distribution matrix that documents and correlates long-term prognoses potentials.

Rational of target-volume concept and dosage prescription
Craniohypophyseal tumors are sharply bordered in the imaging. In contrast to primary brain tumors, they clearly tend towards less infiltrative growth, permitting a small safety margin of ca. 5 mm maximum. Their pathobiological characteristics allow the option of using high-precision, 3-dimensional conformation technology. However, very little detail exists in the literature regarding the necessary irradiation dosage. Regine et al. did report a 50% relapse rate for doses < 54 Gy compared to 15% following doses > 54 Gy using conventional fractionated irradiation (Regine et al. 1992). With a tolerance dosage (TD) of adjacent optical tract of TD 5/5 for ca. 56 Gy, this application of the target-volume dosage concept means no unjustifiable risk to acuity or field-of-vision impairments (bitemporal hemianopsia). A conventional fractionated irradiation target (total) volume dose of 54 Gy has therefore been established worldwide.

Fractionated percutaneous radiation therapy is the most well-established radiooncological procedure for treating craniohypophyseal tumors. Regarding the aims of this study, the relevant technology is conformable-dose fractionated percutaneous radiation therapy. KRANIOPHARYNGEOM 2007 recommends that the reference center (Dept of Radiooncology, University Leipzig, Germany) should be consulted when alternative radiooncological method(s) are considered.
2.9.1 Intensity modulated radiation therapy (IMRT)
Intensity modulated radiation therapy (IMRT) is an advanced application of three dimensional computer tomography (CT) whereby conformal irradiation achieves results using several beam directions of different intensities. IMRT applies "inverse irradiation planning" so to speak. The irradiation plan calculates computer-determined desirable doses based on variable tumor tissue response as well as tolerable doses for adjacent normal structures.

2.9.2 Stereotactic gamma knife radiosurgery (y-knife)
Stereotactic gamma knife radiosurgery enables the application of high, single-dose irradiation. Experience with stereotactic gamma knife radiosurgery (y-knife) for primary or relapse craniopharyngioma surgery is minimal. The minimum applied dosage is between 9 and 20 Gy and significant visual deteriorations are reported in 10 to 66% of cases following y-knife treatment. Radio gene damages to the optic nerve from y-knife treatment can be avoided by using conventional radiation therapy. It is recommended to restrict y-knife treatment to patients with small (<2 cm) craniopharyngiomas that are 5 mm or more away from the optic chiasm (Lunsford 1994). A y-knife surgical treatment is not recommended for patients with predominantly cystic craniopharyngiomas (Kobayoshi 1994). Tumor control rates of 70–100% were reported 1–5 years after gamma knife radiosurgery. It is the view of this study's commission that stereotactical single-dose convergence irradiation (e.g. linear accelerator or gamma knife radiosurgery) is of little or no value in treating craniopharyngiomas based on radiation biology reasons. However, to what extent stereotactic single-dose convergence irradiation as a primary or ancillary treatment can be utilized in individual cases of very small residual tumors or an R1 situation in a clearly-delineated area has yet to be clarified.

2.9.3 Intracavitary beta radiation of cystic craniopharyngiomas
As an alternative experimental therapy option, stereotactic instillation of radioisotopes (32Phosphor in USA, 89Yttrium in Europe and Japan, 198Gold and 186Rhenium in some other countries) – mainly for monocystic craniopharyngioma recurrences – has been discussed (Lunsford 1994). The radiation induced fibrosis and functional suppression of cyst fluid production is postulated as the pathophysiological mechanism. Degeneration of the cyst can be achieved 80–88% and a 5-year survival rate of 80% is reported (Voges 1997). Twenty-five (25) patients had intracavitary 32P therapy tumor/cyst control rates of 76% after 5 years and 70% after 10 years respectively. Vision either improved or stabilized in 48% of patients. Intact endocrine function in 48% of patients was unimpaired, even after their intracavitary 32 phosphor therapy (Hetelekidis 1993). Neither acute complications nor cyst leakage appeared in this patient series. Nevertheless, this treatment method is restricted to cystic craniopharyngiomas and should be considered only for postoperative recurrences and after percutaneous radiation therapy.

2.9.4 Proton therapy
The feature of proton radiation therapy is that protons, decelerated through collision with electrons, enter the tissue. Radiation dose is then increased to a so-called Bragg peak, a dosage velocity that can reach as deep as 38 cm and is deposited into the tumor tissue. Practically no residual radiation remains afterwards. With this method, a better radiation dose distribution is achieved relative to required target volume compared dose energy levels of conventional radiation therapy. Based on their energy absorption profile, protons offer a higher conformability compared to three dimensional computed tomography (CT) or MRI, therefore enabling a more protective irradiation method for the surrounding normal tissue. Proton therapy appears to be a therapeutic option for low malignant brain tumors and especially for craniopharyngiomas localized in the vicinity of the optic nerve or chiasm, pituitary gland, or hypothalamus. Preliminary experiences with proton therapy applied to craniopharyngiomas appear to be very promising (Baumert 2004).
2.10 Chemotherapy
Systemic chemotherapy approaches have no role in the treatment of craniopharyngioma tumors because histologically they present as brain tumor with low grade of malignancy (WHO I) and they are better characterized as a dysplasia (Hargrave 2006).

2.10.1 Instillation of sclerosing substances
Due to the favourable therapeutic responses of cystic lymphangioma to intralesional bleomycin instillation that have been reported (Yura 1977, Okada 1992), this focal chemotherapeutic approach was assessed for craniopharyngioma patients. Instillation of sclerosing substances (bleomycin) in craniopharyngioma cysts using an intracystic catheter implanted by a stereotactic or open procedure is a useful therapeutic method mainly for cystic recurrent tumors whose difficult anatomical configuration makes them difficult to resect (Cavalheiro 1996). Radiological exclusion of a cyst leakage after instillation of contrast medium is required before instillation of bleomycin. It is also important that the cyst membrane be of sufficient thickness. Cavalheiro et al. performed an instillation of 10 mg bleomycin daily over 8 days before cyst fluid was fully aspirated. This led to complete remission of the cystic craniopharyngioma in this particular patient. Curbing solid tumor component growth using instillation of sclerosing substances in cystic tumors is not to be expected. Takahashi et al. treated 7 craniopharyngioma patients (ages 2–13 years) two weeks following biopsy and implanted an Omaya reservoir agent instillation of bleomycin (1–5 mg/every 2nd day; cumulative dosage range 13–95 mg). Only the cystic craniopharyngiomas responded (n=4). Patients with predominantly or exclusively solid tumors (n=3) also undergoing Omaya reservoir instillations of bleomycin showed no treatment response (Takahashi 1985). Studies on dosage-effect relationships and especially cyst volume dosage dependencies have yet to be published.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Dosage per day (mg)</th>
<th>Max. Dosage (mg)</th>
<th>Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takahashi, 1985</td>
<td>1–5</td>
<td>95</td>
<td>every 2nd day</td>
</tr>
<tr>
<td>Broggi, 1994</td>
<td>3–5</td>
<td>42</td>
<td>every 2nd day</td>
</tr>
<tr>
<td>Cavalheiro, 1996</td>
<td>10</td>
<td>80</td>
<td>Daily</td>
</tr>
<tr>
<td>Zanon, 1998</td>
<td>2–10</td>
<td>60</td>
<td>every 2nd day</td>
</tr>
<tr>
<td>Hader, 2000</td>
<td>2–5</td>
<td>115</td>
<td>every 2nd day</td>
</tr>
<tr>
<td>Savas, 2000</td>
<td>7</td>
<td>56</td>
<td>Daily</td>
</tr>
<tr>
<td>Mottolese, 2001</td>
<td>3</td>
<td>150</td>
<td>every 2nd day</td>
</tr>
<tr>
<td>Alen, 2002</td>
<td>5</td>
<td>75</td>
<td>every 2nd day</td>
</tr>
<tr>
<td>Park, 2002</td>
<td>2–5</td>
<td>180</td>
<td>2–7 days</td>
</tr>
<tr>
<td>Jiang, 2002</td>
<td>5</td>
<td>120</td>
<td>Daily</td>
</tr>
<tr>
<td>Hernandez, 2002</td>
<td>5</td>
<td>84</td>
<td>2 × per week</td>
</tr>
<tr>
<td>Caceres, 2005</td>
<td>5</td>
<td>60</td>
<td>weekly, every 2nd day</td>
</tr>
</tbody>
</table>

Table: literature survey of therapy modalities for intracystic application of bleomycin in cystic craniopharyngiomas (Caceres 2005).
Table: literature survey of therapy modalities for intracystic application of bleomycin in cystic craniopharyngiomas (Caceres 2005).

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>Follow-up observation (years)</th>
<th>Progression-free survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takahashi, 1985</td>
<td>7</td>
<td>5</td>
<td>57</td>
</tr>
<tr>
<td>Broggi, 1994</td>
<td>19</td>
<td>7</td>
<td>43</td>
</tr>
<tr>
<td>Frank, 1995</td>
<td>6</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cavalheiro, 1996</td>
<td>1</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Sagoh, 1997</td>
<td>1</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Zanon, 1998</td>
<td>21</td>
<td>1–6</td>
<td>61</td>
</tr>
<tr>
<td>Hader, 2000</td>
<td>7</td>
<td>2.5</td>
<td>57</td>
</tr>
<tr>
<td>Mottolese, 2001</td>
<td>18</td>
<td>1–6</td>
<td>94</td>
</tr>
<tr>
<td>Alen, 2002</td>
<td>1</td>
<td>1.5</td>
<td>100</td>
</tr>
<tr>
<td>Park, 2002</td>
<td>10</td>
<td>2.8</td>
<td>60</td>
</tr>
<tr>
<td>Hernandez, 2002</td>
<td>4</td>
<td>3.2</td>
<td>50</td>
</tr>
<tr>
<td>Jiang, 2002</td>
<td>9</td>
<td>0.5–2</td>
<td>80–100</td>
</tr>
<tr>
<td>Caceres, 2005</td>
<td>2</td>
<td>8</td>
<td>100</td>
</tr>
</tbody>
</table>

Favourable compatibility and effectiveness of instillation of alpha-interferon in craniopharyngioma cysts has recently been reported (Cavalheiro 2005).

2.11. Endocrinology

2.11.1 Hormonal deficiencies

Postoperative disturbances occur in the majority of cases (85–95%) independent of the degree of resection, with multiple hypothalamic-pituitary deficits as severe as panhypopituitarism (DeVile 1996, Halac 2006). Only in exceptional cases does a full restoration of preoperative hormonal deficits following craniopharyngioma resection occur (Honegger 1999).

2.11.2 Growth

Growth hormone deficiency is presented in ca. 75% of cases at the time of diagnosis. Studies on growth rates based on data from provisional investigations yielded significantly reduced growth rates initiating at infancy (H.L. Müller 2004). The effectiveness and safety of growth hormone substitution in craniopharyngioma patients with hypothalamic-pituitary deficiency is documented in several studies (Price 1998; Hogeveen 1997). In spite of quantified GH deficiency and even without growth hormone substitution, some patients present with normal to accelerated growth rates whose extreme weight gain often leads to obesity. The pathogenesis of this phenomenon remains unclear. Discussions exist in the literature regarding secretion disturbances of prolactin, insulin, and/or insulin-like growth factor-I (Bucher 1983; Finkelstein 1972; Geffner 1996). As of yet, there are no reports of prospective studies regarding to what extent early GH substitution influences the incidence and degree of postoperative obesity.

2.11.3 Pubertal development

Gonadotropin deficiency represents the most common pathological symptom in adult craniopharyngioma patients (Pajas 1995). Up to 100% of affected adolescents present pubertal disturbances at the time of diagnosis (de Vries 2003). Diagnosis of gonadotropin deficiency in the prepubescent child is impeded by low sensitivity of the GnRH assays due to low physiological basal LH and FSH values at prepubertal stages. GnRH stimulation testing studies estimated that ca. 85% of prepubertal craniopharyngioma patients present with gonadotropin deficiency (de Vries 2003). While it is evident that most adolescents present with overdue onset of puberty, some patients present with precocious puberty (as defined in boys: pubic arch <9 years of age; in girls: pubic arch <8 years). Banna et al. (1973) reported precocious puberty in three adolescent boys ages 3, 4 and 7 at the time of their craniopharyngioma diagnosis.
2.11.4 Secondary / tertiary hypothyroidism
Hypothyroidism is assessed in 2.7–24% of patients at diagnosis and in 29–85% following resection combined with irradiation (Halac 2005). Clinical signs of hypothyroidism are cold intolerance, constipation, dry skin, reduced physical activity and bradycardia. Secondary (pituitary) and tertiary (hypothalamic) hypothyroidism are both characterized by decreased TSH levels with low free \( T_4 \) in serum and \( T_4 \) concentrations respectively. Patients with tertiary hypothyroidism present an attenuated TSH increase after TRH (Gruneiro-Papendieck 1998).

In laboratory diagnostic monitoring conditions, anticonvulsant therapy using carbamazepine disrupts hypothyroidism. Several assays measured lowered values for free and total \( T_4 \) under carbamazepine medication using dialysis and/or ultrafiltration assays of \( T_4 \) measurements to such a favourable extent that its application is recommended.

2.11.5 Diabetes insipidus neurohormonalis (DI)
DI is presented in 9–38% patients at the time of craniopharyngioma diagnosis (Sklar 1994; Pajas 1995). The appropriate pharmaceutical treatment of DI by means of desmopressin acetate (DDAVP), is important in minimizing its perioperative morbidity and mortality (Lehrnbecher 1998). The postoperative DI rate is 76–94% (Leyen 1982; Halac 2005).

2.11.6 Hypocortisolism
An ACTH deficiency with secondary hypocortisolism was assessed in 25–71% of patients at the time of diagnosis. An ACTH deficiency was demonstrable in 72% of patients postoperatively examined using provocation testing.

2.11.7 Obesity and eating disorders
Hyperphagia and obesity are observed on average in about 50% of craniopharyngioma patients (Curtis 1994). The study results vary from 6% (Galatzer 1981) to 91% (Imura 1987). The incidence of severe obesity in children and adolescents following craniopharyngioma resection surgery is somewhere between 22 and 62% (Brauner 1987; Sorva 1988).

Disturbance of the hypothalamus, especially a lesion in the area of the ventromedial hypothalamus by the tumor itself and/or its radiation/surgical treatment, or invasion and/or treatment disturbance of neighbouring brain structures have all been discussed as major causes of hyperphagia and obesity. An influencing role of the ventromedial and lateral hypothalamus in controlling eating habits was confirmed in animal investigative studies (Anand 1962; Albert 1991; Eclander 1971). The cause of “hypothalamic obesity” is attributed to a stimulation of the “hunger center” in the lateral hypothalamus caused by injury to the “satiety center” in the ventromedial hypothalamus (Stellar 1954; Blundell 1982; Blundell 1990).

This purely neuroanatomical model has been supplemented by neurochemical augmentations outling the significance of neurotransmitters, neuromodulators and peripheral hormones in the control of eating habits (Stricker 1978). Gold (1973) postulated that injury to the ventromedial hypothalamus affecting the ascending noradrenaline rostral system can cause hyperphagia. Ahlskog (1975) then proposed that the extent of hyperphagia is especially serious if both the hypothalamic ventromedial nucleus and the corresponding noradrenaline uptake system are damaged. The noradrenaline system is ascribed a particularly key roll in the initiation of eating while the serotonergic system seems to be of importance to satiety and limiting eating via stimulation to the ventromedial hypothalamus (Leibowitz 1987; 1988). Especially the ventromedial, paraventricular, and medial hypothalamic suprachiasmatic nucleus show particular sensitivity to serotonergic stimulation (Leibowitz 1990). In a study by Jordaan, Roberts & Emsley (1995), treatment of hyperphagia and obesity with serotonergic agonists (fluoxetine and fenfluramine) appeared ineffective. The authors attributed this to the destruction of serotonin-sensitive hypothalamic receptors.

Roth and colleagues (1998) measured postoperative serum leptin levels in craniopharyngioma patients (n=14) and found significantly elevated leptin concentrations relative to body mass index (BMI) in patients with a suprasellar tumor component, while patients with exclusively sellar tumor localization displayed low leptin levels. They postulated that a possible pathogenic factor for obesity in craniopharyngioma patients is a disruption to the feedback loop process between leptin formed in adipocytes and the hypothalamic receptors for leptin. A missing appetite inhibition as a consequence of deficiency in this leptin regulation mechanism was reported by Brabant and colleagues. They were able to show in a small craniopharyngioma patient cohort that postoperative serum leptin concentrations increased disproportionately to excessive weight gain (Brabant 1996). No prospective studies have yet been published on pre- vs. postoperative obesity in craniopharyngioma patients.
Analyses of nutritional diaries yielded no significant differences in caloric intake between craniopharyngioma patients and normal controls (Harz 2003). In an accelerometric investigation, limited physical activity in craniopharyngioma patients was observed, especially for those with tumors invading the hypothalamus or otherwise hypothalamically involved.

DeVille (1996) classified the extent of hypothalamic injury in 63 patients by means of imaging procedures (MRI), ranging from 0 (no injury) to 2 (seriously injured). It appeared that the larger the classified extent of hypothalamic damage, an even greater deviation in BMI occurred. In only 7 patients no BMI deviations were detectable. Of the 17 children with severe hypothalamic disruptions, 10 experienced extreme weight gains, all of whom the imaging investigations were able to confirm had had an extensive hypothalamic tumor invasion.

Obesity in craniopharyngioma patients is frequently accompanied by eating disorders. The therapy of eating disorders in affected patients is difficult due to limited reports on effective treatment modalities. No prospective studies have yet been published on the incident rates, characteristics and therapies for craniopharyngioma eating disorders.

2.11.8 Laparoscopic adjustable gastric banding (LAGB)
As an accompanying pilot study to the multicenter surveillance study of children and adolescents with craniopharyngioma (KRANIOPHARYNGEOM 2000), four severely obese patients were treated with laparoscopic adjustable gastric banding (LAGB) to reduce their weight. Patients were monitored with respect to BMI and eating habits following this bariatric intervention. Craniopharyngioma were diagnosed in the four patients at 2, 11, 12, and 18 years of age. BMI SDS at the time of diagnosis was -0.8, +2.3, +4.7 and +0.1SD respectively using the Rolland-Cachera classification method. The patients developed severe obesity (BMI SDS: +13.9, + 9.3, +11.4, +7.3). Gastric banding procedures were performed 11, 6, 9 and 3 years respectively following their craniopharyngioma diagnoses. Laparascopic intervention and postoperative progress monitoring revealed no complications. Follow-up observations 3.5, 0.3, 1.0, and 0.5 years after LAGB showed BMI reductions of around 7.0, 0.4, 3.7, and 1.8 SDS respectively. The BMI-SDS reductions occurred slowly and steadily, patient eating habits after gastric banding fundamentally changed, and their pre-existing hunger attacks declined immediately and considerably. Deterioration of their psychological behaviour was not indicated. We conclude that bariatric intervention such as LAGB might a viable therapy option for weight reduction in craniopharyngioma patients when hypothalamic injury-induced eating disorders are presented (H.L. Müller 2006). Further observations assessing long-term success as well as studies regarding the role of gastrointestinal hormones in craniopharyngioma weight regulation are planned. Of special interest is the hypothesis that “functional vagotomy” performed by LAGB might have pathogenic influence on the rapid postoperative change in hunger sensation, which can cannot explained by the mechanical effects of LAGB on gastric passage.

2.11.9 Medical therapeutic approaches to hypothalamic obesity
Injury to the ventromedial hypothalamus leads to hyperphagia, obesity, hyperinsulinism and insulin resistance in a rat animal model (Sorva 1988; Jeanrenaud 1985; Powley 1981). As pathogenic causes of hypothalamic obesity, direct damage to neural mechanisms of appetite regulation and/or disinhibition of vagal output leading to hyperinsulinism secretion of pancreatic beta cells have been postulated (Jeanrenaud 1985; Ionescu 1983; Bray 1979).

2.11.10 Sympathetic outflow – catecholamine metabolites in urine
Craniopharyngioma patients often develop obesity, daytime sleepiness and diminished physical activity. Roth et al., 2006, examined whether a hypothalamic lesion from craniopharyngioma and/or surgery plus immediate irradiation lead to reduction of central sympathetic outflow and physical activity. Catecholamine metabolites vanillmandelic acid (VMA) and homovanillic acid (HVA) were measured in morning urine of 93 children and adolescents with craniopharyngioma (KRANIOPHARYNGEOM 2000) and compared to an age-matched control group. Physical activity was evaluated by means of a questionnaire. Obese children and adolescents with craniopharyngioma (BMI>2SDS) presented lower HVA and VMA levels as well as lower activity scores compared to patients with a normal BMI (BMI<2SDS). In patient urine with hypothalamic tumor involvement (BMI-SDS: 4.3±0.4), VMA excretion (VMA\_CP/VMA\_control 0.81±0.06) as well as HVA excretion (HVA\_CP/HVA\_control 0.77±0.06) were markedly reduced compared to craniopharyngioma patients without hypothalamic tumor involvement (CP) (BMI-SDS: 1.4±0.3; VMA\_CP/VMA\_control 0.88±0.05; HVA\_CP/HVA\_control 1.06±0.07) (p<0.01;p<0.01). Patients with hypothalamic tumor localization had significantly (p<0.01) lower activity
scores compared to craniopharyngioma patient activity scores without hypothalamic tumor involvement. These results support the speculation that disturbed central sympathetic adrenal regulation caused by hypothalamic tumor localization can lead to reduced physical activity and obesity in craniopharyngioma patients with hypothalamus injury. A disturbed sympathetic outflow as a pathogenic factor and possible starting point should be taken into consideration when searching for therapeutic responses to hypothalamic obesity.

2.11.11 Amphetamines
Mason et al. (2002) treated 5 craniopharyngioma patients (ages 6–9.8 years) with dextroamphetamine for 24 months – all patients having had hypothalamic craniopharyngioma involvement and pronounced postoperative weight gain. Initial dosage was 5 mg administered in the morning. Dosage was increased 2.5 mg weekly until the desired therapeutic effects (appetite reduction and activity increase) were obtained or a side-effect appeared. Amphetamine therapy stabilized patient BMI and parents reported noticeable improvements in their child’s physical activity and alertness.

2.11.12 Somatostatin analogues (Octreotide®)
The effect of 6-month therapy with a somatostatin analogue (Octreotide®) on insulin secretion and weight gain was examined in an open, non placebo-controlled study of 9 patients with distinct damaged-hypothalamic obesity (Lustig 1999). These patients presented excessive hypothalamic injury-induced hyper insulin secretion that significantly diminished with regular, daily, subcutaneous administration of (Octreotide®) (initial dose: 5 µg/kg/d in 3 ED, end dose: 15 µg/kg/d in 3 daily doses. Their weight gain remained static in the first two months of therapy; in months 3–6 significant (p=0.0004) weight loss occurred (ΔBMI: -2.0 ± 0.7 kg/m² [range: -4.7 – +0.8 kg/m²]). Five of the 8 patients lost weight, 3 patients stabilized their body weight. After a month of Octreotide® therapy, one patient with craniopharyngioma developed oedemas causing therapy to be prematurely discontinued. Lustig et al. (2003) treated 18 craniopharyngioma patients in a double blind, placebo-controlled setting with Octreotide® dose escalation therapy. In the first two months of therapy, the Octreotide® group lost weight but cause-and-effect interpretations were impeded by initial gastrointestinal side effects (nausea and diarrhoea). After their initial side effects diminished, weight increases in the 3rd and 4th months were detected. Not until the 5th and 6th months did their weight and BMI reduce compared to the placebo group, whose weights actually increased.

<table>
<thead>
<tr>
<th>Months 0–2</th>
<th>Months 2–4</th>
<th>Months 4–6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octreotide® dosage:</td>
<td>5 µg/kg/d</td>
<td>10 µg/kg/d</td>
</tr>
<tr>
<td>Weight change (kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Octreotide® (n=9)</td>
<td>0.08±0.54</td>
<td>1.96±1.36</td>
</tr>
<tr>
<td>Placebo (n=9)</td>
<td>3.60±1.05</td>
<td>2.44± 0.44</td>
</tr>
<tr>
<td>Difference (Octr. vs. placebo)</td>
<td>-3.52±1.18</td>
<td>-0.48±1.36</td>
</tr>
<tr>
<td>BMI change (kg/m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Octreotide® (n=9)</td>
<td>-0.08±0.27</td>
<td>0.59±0.47</td>
</tr>
<tr>
<td>Placebo (n=9)</td>
<td>1.19±0.31</td>
<td>0.28±0.19</td>
</tr>
<tr>
<td>Difference (Octr. vs. placebo)</td>
<td>-1.27 0.41</td>
<td>0.31±0.49</td>
</tr>
</tbody>
</table>

Table: Execution and results of randomized Octreotide® Study (Lustig 2003)
It is important to emphasize that fluid displacement affected by DDAVP therapy must be considered when using BMI as a measurement for obesity in patients with diabetes insipidus.

### 2.11.13 Melatonin
Distinct daytime sleepiness accompanied by interferences in circadian rhythm has been documented in craniopharyngioma patients (H.L. Müller 2004). Müller et al. studied 115 children and adolescents with respect to the degree of daytime sleepiness using a German version of the Epworth Sleepiness Scale (ESS). Thirty-five of the patients (30%) presented ESS point values > 10, indicating severe daytime sleepiness; fourteen of these 35 patients were obese. Twenty-six percent (26%) of the obese patients had ESS scores > 10 points. Patient daytime sleepiness and obesity correlated with low nighttime melatonin levels. A disruption to hypothalamic regulation of circadian rhythms synchronized by melatonin caused by suprasellar craniopharyngioma is postulated as a pathogenic mechanism. Initial experiences with melatonin substitution (6mg/day) yielded an increase in average physical activity levels and normalization of circadian rhythms as well as melatonin levels (H.L. Müller 2006).

### 2.11.14 Modafinil treatment of secondary narcolepsy
Ten obese patients displaying severe daytime sleepiness were analyzed using polysomnography (PSG) and Multiple Sleep Latency Tests (MSLT). PSG analysis revealed two craniopharyngioma patients with an obstruction of their upper respiratory tract (obstructive sleep apnoea syndrome). MSLT revealed four patients experienced repeated episodes of SOREM (sleep onset rapid eye movements), SOREM representing the PSG-confirmed diagnostic condition for secondary narcolepsy. Three more patients displayed typical hypersomnia. All but one of the obese patients suffered from severe obesity. A small group of the obese craniopharyngioma patients revealed PSG-confirmed secondary narcolepsy whose treatment with central stimulating agents showed a significant beneficial effect (modafinil 100 – 400 mg/d, methylphenidate 10 – 30 mg/d) (H.L. Müller 2006). We conclude that secondary narcolepsy should be taken into consideration as a post craniopharyngioma pathogenic factor in severely obese children and adolescents with craniopharyngioma. Recent reports on the hypothalamic dysregulation of orexin production and metabolism in patients with idiopathic narcolepsy support this hypothesis.

### 2.11.15. Sibutramin
Sibutramin is an appetite suppressant and is classified as a serotonin-noradrenaline selective reuptake inhibitor. According to the manufacturer’s statement, sibutramin diminishes nutritional energy intake by evoking satiation sensation. Concurrent with these effects, sibutramin is said to increase energy utilization via thermogenesis. Side-effects are, among others, increased blood pressure, increased heartbeat rate, nausea, dryness of mouth and constipation. This medication is available only by prescription and is used for treating patients with nourishment-contingent excess weight and BMI over 30 kg/m$^2$ or in excess of 27 kg/m$^2$ when accompanied by additional risk factors. No studies have yet been published on the effectiveness and appropriateness of treating obese craniopharyngioma patients with sibutramin.

### 2.11.16. Orlistat
Orlistat is the saturated derivative of natural lipstatin and inhibits lipase-enabling absorption of fats in the small intestine. According to the manufacturer’s statement, its appr. 30% intended reduction in fat absorption is cause by fast stool elimination. Nutritional fat intake serves as the primary source of energy for the body. Side effects of orlistat are, among others, diarrhoea due to high fat content in the stools when a low-fat diet is not practiced. Moreover, the absorption of desirable nutritional ingredients such as essential fat soluble vitamins A, D, E and K is diminished. Orlistat is only available by prescription (in Germany) and is appropriate for treating those whose BMI is over 30 kg/m$^2$ or when BMI is over 28 kg/m$^2$ accompanied by disease sequelae associated with obesity. No studies have yet been published on the effectiveness and appropriateness of treating obese craniopharyngioma patients with orlistat.
2.11.17 Rimonabant – a selective CB₁ receptor antagonist
The endocannabinoid system (EC system) consists of cannabinoid receptors, two subtypes to be described here. CB₁ receptors occur at a higher density in the CNS (small brain, basal ganglions, and hippocampus) and at a lower density in peripheral tissues. The CB₂ receptor is characteristically present in immune system cells. Increased activity of the EC system is associated with excess weight and nourishment intake. Rimonabant selectively blocks the CB₁ receptor and is (in addition to diet and physical activity) advisable for treating the obese whose BMI is over 30 kg/m² or over 27 kg/m² with at least one accompanying sequelae associated with obesity. No studies have yet been published on the effectiveness and appropriateness of treating obese craniopharyngioma patients with rimonabant. According to manufacturer, rimonabant treatment is not recommended for children and adolescents. Recently, Rimonabant was taken from the german market due to psychological adverse side effects.

2.11.18 Dehydroepiandrosterone sulfate (DHEAS)
Dehydroepiandrosterone (DHEA) and its sulfated ester dehydroepiandrosterone sulfate (DHEAS) are quantitatively the most prevalent steroidal products produced by the human adrenal cortex. In contrast to cortisol which displays a circadian rhythm but otherwise constant lifelong secretion, DHEA also has a cortisol-like circadian rhythm but its secretion is regulated by age with markedly different age-related serum levels (Orentreich 1984). DHEAS serum secretion commences between ages 6 to 8 y, initiating the so-called adrenarche. The adrenarche climbs, peaking at around age 20 y, then progressively decreasing from age 35 y until age 50–70 y, eventually stabilizing at a low level ("adrenopause").

Both DHEA regulation and its exact physiological significance are relatively unexplored in comparison to cortisol. The basic effect mechanism of DHEA is characterized by the following two features:

• First, DHEA appears to be transcribed into highly activated metabolites in the target cells of the respective peripheral target organs, a process known as "intracrinology" (Ebeling 1994).
• Furthermore, there is both in vitro and in vivo evidence that DHEA via its peripheral conversion to metabolites can yield either an estrogenic or androgenic effect depending on the hormonal milieu (Labrie 1991).

The varying age-related DHEA and DHEAS serum concentrations suggest a role these hormones may have in the regulation of growth and proliferation mechanisms. Epidemiological studies have also referenced a positive DHEAS effect on bone density. As indicated by large epidemiological studies that found low DHEAS levels positively correlated with an increased cardiovascular morbidity, DHEA may play an important role in the origin and/or prevention of atherosclerotic processes by influencing insulin secretions such as lipoprotein lipase (Barnett-Connor 1986). An in vitro DHEA-induced stimulation of IL-2 production via activated T lymphocytes has been documented, suggesting another immunomodulating effect of DHEA. The presence of DHEA in brain tissue has also been documented, in vitro tests displaying GABA-agonist as well as anti GABA-agonist effects resembling neurosteroid effects. In clinical studies on DHEA-deficient subjects, DHEA substitution displayed subjective influences on participants' well-being factors such as sleep habits. Conclusive clinical significances of DHEA such as the molecular bases for its regulation and effects are actively being researched (Allolio 1996).

In spite of very promising therapiic approaches, it must be emphasized that at present, no acknowledged, pharmaceutical therapy exists for obesity in children and adolescents with craniopharyngioma.
2.11.19 Bone density – osteoporosis

Due to hormonal deficits and consequential endocrine substitution therapy, craniopharyngioma patients are at risk for developing osteoporosis. We examined 61 child and adolescent patients averaging 5.4 years of age (0.5–19 y) following their craniopharyngioma diagnosis for risk factors of reduced bone mineral density (BMD), obesity and diminished QoL.

Z scores of distal radius and spongiosa BMD of the patients (29f/32m, average age 15 y, 5–32 y) and 14 age-comparable controls (7f/7m) were measured by means of peripheral quantitative computed tomography (pQCT). BMD changes as well as endocrine parameters were co-examined. QoL was determined using FMH, the German-developed functional abilities assessment questionnaire (Fertiheitsenskala Münster Heidelberg).

Patient Z scores were reduced (distal radius average: -1.5; range: -3.1–1.4; spongiosa bone average: -0.4; range: -2.4–2.3) in comparison to controls (distal radius: -0.6; -1.5–2.1; spongiosa bone: 0.0; -2.2–2.6) (p<0.05). Patients (n=23) with severe obesity (BMI>4SD) had a higher BMD (p<0.05) than normal weight (BMI<2SD) patients (n=38); male patients (n=32) had a lower BMD than female patients (n=29) (p<0.01). Group differences were not demonstrable regarding age and pubertal stage at the time of the study nor diagnosis, duration and dose of hormone substitution therapy, endocrine parameters, and parameters of bone metabolism. Patient QoL correlated with their degree of obesity (BMI SDS, r:-0.44; p <0.001) but not with BMD. Test results showed normal-weight male craniopharyngioma patients were at a higher risk for reduced BMD and should therefore be monitored regularly using pQCT (H.L. Müller 2003).

2.12 Ophthalmological findings

In a French study series of craniopharyngioma patients (I.S.P.C.91), 42% were vision-impaired at the time of diagnosis; impairment was moderate in 17% and severe in 25%. Partial paralysis of the optic nerves was observed in 8–13% of cases at diagnosis, partial paralysis of the abducens nerve and trochlear nerve being the exception (Choux 1991). Ophthalmoscopy performed at time of a craniopharyngioma diagnosis revealed papillary atrophy in 35–45% cases, and papilledema in somewhat fewer cases (20–35%). Field of vision was impaired (bitemporal hemianopsia) in 36% of cases at the time of craniopharyngioma diagnosis and normal in 30% of patients at the time of diagnosis in a meta analysis of 23 published series.

A retrospective analysis of 371 childhood craniopharyngioma patients yielded a postoperative improvement in 61% of cases compared to their preoperative vision, whereas 13% of cases presented a worsening of vision (Choux 1991). Postoperative ophthalmologic conditions and developments must be appraised and are dependent upon the surgical strategy (total vs. partial resection), case history duration and pre-existing deficiencies, yet the literature is often difficult to interpret. Hoffmann et al. studied pre- and postoperative patient vision acuity and found improved postoperative vision in 66% of cases following microsurgical complete resection, 46% following incomplete resection, and in 1 of 6 cases following tumor biopsy (Hoffmann 1977). Cabezudo et al. registered a postoperative vision improvement for 87% of those with preoperative case history duration of under 12 months, whereas only 33% with longer case history durations experienced improved vision (Cabezudo 1984). In some studies, significant postoperative ophthalmologic differences between children and adults were not demonstrable (Cabezudo 1984; Yasargil 1990). Yet other studies demonstrated an age dependency regarding comparatively worse ophthalmologic outcomes in children under 6 years of age (Abrams 1997).

The interpretation of most studies is difficult because differentiations between children and adults are frequently lacking (Yasargil 1990; Van den Berge 1992) and preoperative conditions often do not exist at all (Abrams 1997) and/or there is no quantification of the study parameters (Sorva 1988; Baskin 1986). Prospective studies of ophthalmologic long-term side effects vis-à-vis different therapy modalities have yet to be published.
2.13 Neuropsychological deficiencies

Animal studies have demonstrated that electrical stimulation of the amygdala, septal nuclei and posterior hypothalamus causes aggression attacks and intermittent, explosive behaviour (King 1954). Cat models showed that electrical stimulation of the posterior lateral hypothalamus can lead to hyperphagia in addition to the above mentioned aggressive behaviour attacks. It turned out that several cases where the ventromedial nucleus was affected resulted in both hyperphagia and disinhibited aggressive behaviour (Flynn 1988; Reeves 1969; Haugh 1983).

In humans, hypothalamic lesions can lead to emotional lability, fury attacks, abnormal sexual behaviour, and deficits in memory and intellectual capacities (Bauer 1954; Bray 1975). Flynn (1988) reports a neurobehavioral syndrome with the four main symptoms: (1) episodic rage attacks, (2) emotional instability, (3) hyperphagia with attendant obesity, and (4) intellectual impairment. According to Flynn, this syndrome is especially attributed to lesions of the ventromedial nucleus. Flynn also states that thus far, attempted treatments of this neurobehavioral syndrome such as high doses of an antipsychotic neuroleptic and/or psychotherapeutic behaviour interventions are ineffective.

Related to this work, Cohen has documented observed problems in the area of attention spans and deficits in impulse control and motivation (Cohen 1991). Children with tumors of the third ventricle display symptoms of amnesia, confusion and vigilance impairment (Ellenberg 1987). Lesions of the ventromedial prefrontal cortex whose victims display symptoms of poor impulse control and attention deficits have also been documented (Eslinger 1985). Tonkonogy and colleagues (1992) attribute the posterior hypothalamus and its relationship to components of the limbic system a pathogenic relevance because socialized inhibition of aggressive behaviour is regulated in these areas. In the opinion of these authors, aggressive behaviour attacks are due to tumor size and/or scar tissue-disrupted connections between the posterior hypothalamus and limbic system from surgical intervention.

The literature on neuropsychological conditions of craniopharyngioma patients appears to be controversial based on a small investigative collective and a variety of study methodologies (Riva 1998). Data on preoperative neuropsychological conditions are rare and studies on postoperative, neuropsychological outcomes are frequently extremely difficult to interpret in the absence of preoperative baseline investigations. Comparative evaluations of pre- and postoperative neuropsychological deficits are the key to planning surgical strategies (gross total resection vs. partial resection plus immediate irradiation) in regard to long-term QoL effects.

The predominant indicator found in the literature is postoperative normal intelligence quotients for adult craniopharyngioma patients (Clopper 1977; Hoffman 1992), yet only anecdotal reports have been published on diminished postoperative intelligence results (Katz, 1975; Weiss 1989). Honegger and colleagues prospectively studied a small cohort (n=13) of adult craniopharyngioma patients following mostly transsphenoidal resections and found no impairments regarding their neuropsychological status (Honegger 1998). However, several studies of children with craniopharyngioma yielded disturbances of memory, attention, impulse control, motivation and socialization (Stelling 1986; Colangelo 1990; Fischer 1985, 1990; Cavazutti 1983; Galatzer 1981). The correlation between cognitive interferences and radical resection remains controversial (Fischer 1990; Anderson 1997). It is generally agreed that neuropsychological consequences following irradiation are dependent upon the child's age, irradiation volume, individual dosages, and the total dosage, as well as illness-contingent and other therapy-associated variables. Neuropsychological deficits appear more serious in patients following relapses and/or relapse surgery (Scott 1994). As of yet there are no published prospective investigations regarding neuropsychological prognoses of children and adolescents with craniopharyngioma.
2.14 Quality of Life (QoL)
Craniopharyngioma and treatment of afflicted children and adolescents means long-term somatic and psychosocial consequences continually affecting their QoL. Additional factors are social reintegration and rehabilitation back into school and occupation, as they impact patients’ long-term life planning. Systematic detection of health-related QoL and long-term consequences has not yet been established. Existing reports are on single-center, cross-sectional investigations of small collectives that provide rough estimates regarding somatic and neuropsychiatric long-term consequences based on the QoL conclusions drawn from the respective studies (Villani 1997). However, as of yet there is no published report on prospective, multicenter study results (self-rated/parents-rated) for health-related craniopharyngioma patient QoL.

An interim analysis of patients recruited in KRANIOPHARYNGEOM 2000 and HIT ENDO verified cross-sectional data yielded the following results: In the HIT ENDO cross-sectional study, 185 children and adolescents were assessed no less than two years after their craniopharyngioma diagnosis by means of questionnaires (KINDL, PEDQOL, EORTC-QIQ-30) regarding their quality of life (QoL). The QoL data were evaluated in reference to grade of resection, irradiation, and body mass index (BMI SDS). In the calculation, 77 complete datasets were evaluated and compared to age-comparable healthy controls. Craniopharyngioma patients self-rated lower QoL scores with respect to PEDQOL domains of cognition and social integration in peer groups. Obese patients (BMI>3SD) rated their body image, physical abilities, and social functioning more negatively than the healthy children did. Emotional function was also more negatively self-estimated by craniopharyngioma patients than the healthy children.

KRANIOPHARYNGEOM 2000 was able to recruit 41 of 70 patients in order to longitudinally evaluate QoL. Most postoperative patients rated their QoL as unrestricted. Yet the postoperative course of the disease portrayed persisting QoL impairments regarding body image, physical abilities and social integration in peer groups. Parents of children with craniopharyngioma estimated the QoL of their child significantly worse, the patients’ self-assessment and their parents’ assessment eventually converging long-term. It can be concluded from these interim results that craniopharyngioma affects the QoL of children and adolescents in factors of endocrine deficits, treatment strategy and obesity. It has also been observed that postoperative QoL changes emerge over time. It is also clear that relevant problems exist regarding social integration into peer groups, acceptance of body image and emotional condition. In view of these varied factors influencing QoL, craniopharyngioma patients require a multidisciplinary care network in order to guarantee successful rehabilitation.

Within the GPOH network of uniform and standardized brain tumor studies (HIT-Leben; project manager: Dr. med. G. Calaminus, Münster; support applied for), future, prospective QoL and life situation detection is planned for children and adolescents with brain tumors. A goal of the HIT-Leben (life) project is to comprehensively document the life situation and QoL of brain tumor patients using self- and parent-rated questionnaires. To support the work of ongoing brain tumor studies, these launched QoL and life situation investigations should to be continuous, collectively collated, and data from newly-initiated brain tumor studies should be correspondingly included. Standardization means that brain tumor patients should be assessed according to prospective longitudinal designs using standard evaluation instruments with identical basis questions. Along with the basis questions are specific questions referencing, for instance, effects of individual tumor entities, or potential moderator/mediator variables such as patient age and sex. In so doing, retrospective analysis utilizing a uniform, already tested structure regarding its characterizing elements such as instruments, communication approaches, infrastructure, data management, etc. is made possible. This targeted standardization is also intended to facilitate overlapping study comparability. KRANIOPHARYNGEOM 2007 data assessment is carried out using standard HIT-Leben guidelines in alignment with the above-mentioned goals.
2.15 Survival rates
Prognosis of children and adolescents with craniopharyngioma in regard to perioperative mortality, percentage of microsurgical complete resections, survival- and event- (relapse) free survival rates, has improved due to advances in surgical techniques and technology over the last 20 years. The literature calculates general mortality rate to be between 8 and 24% after an observation time of 3 to 10 years (Fischer 1990, 1998; Hoffman 1985; Choux 1990). Survival rate is estimated to be between 70 and 100% after 5 years, and between 64 and 96% after 10 years. The reported 5-year relapse-free survival rate was 72±7% and 10-year relapse-free survival rate was 51±9% in a series of 45 craniopharyngioma patients (Sorva 1986).
A large, French study of 370 children with craniopharyngioma yielded no differences in survival rates in relation to the surgical resection grade. In this study, 252 patients had a 10-year survival rate of 92.5% following microsurgical complete resections; 118 patients had a survival rate of 85.6% following incomplete resections; and the group who had incomplete resections plus immediate irradiation (n=88) had a 10-year survival rate of 90% (Choux 1991).
In a comparative study of children vs. adults with craniopharyngioma, the children had higher survival rates and lower perioperative mortality (Wen 1989).

2.16 Perioperative mortality
Surgery mortality has decreased due to advances in surgical technology and anaesthesia procedures. In less recent literature, mortality was reported to be between 0 and 43% with an average of 12% (Choux 1991; Becker 1999). Later literature reported reduced mortality rates of between 1–3% for complete resections performed in high-skill hospitals, achieving comparable mortality rates as for complete resections combined with irradiation (Fahlbusch 1999; Einhaus 1999; Becker 1999). The most frequent perioperative causes of death were haemorrhage, derailment of osmolality regulation, early post-surgery endocrine derailment and infections.

2.17 Long-term mortality
The most frequent causes of late mortality are endocrine deficits and/or derailment. It is important to note that the high rate of deaths caused by infection needs to be considered in the context of accompanying endocrine deficits. The reported mortality rate due to fusiform dilations of the internal carotid artery was 11–15% for patients following resection of various suprasellar tumors (craniopharyngiomas that had grown into more than one cranial fossa). In light of this relatively high mortality rate, surgical alternatives for tumors localized or invading the vascular wall have been adopted (Sutton 1994; Bendszus 1998).

2.18 Late effects of irradiation
The risk of a secondary neoplasm following irradiation of a craniopharyngioma is between 0 and 5%. Secondary neoplasms histologically often involve malignancies such as glioblastoma, sarcoma and meningioma. Reported long-term consequences following craniopharyngioma surgery combined with irradiation are: brain stem necrosis in 1.7%, brain infarcts in 1.7–5%, radiation-induced cerebral vasculitis in 1.7%, and Moya-Moya-syndrome in 2% of the cases (Hetelekidis 1993; Rajan 1993; Sanford 1994; Scott 1994).
Long-term consequences of radiation therapy are generally more intense for children than adults, although this also depends on what section of the brain was irradiated, the volume of brain tissue irradiated, and the fractionated dosage. The precise effects of radiation therapy on children in particular should be more closely examined. As of yet, there are no published reports on prospective studies of long-term irradiation consequences in children with craniopharyngioma, especially ones conducted over a protracted period of time. An integral component of any study on prognoses of craniopharyngioma patients must therefore be the prospective detection of data that illuminates differences in effects of surgical resection alone vs. in combination with radiation irradiation.

A systematic, standardized post-treatment care and documentation program (RISK) for long-term radiation therapy consequences in children and adolescents, working in concert with the German taskforce of pediatric radiooncologist (APRO), has been integrated into the KRANIOPHARYNGEOM 2007 post-treatment care program.
3. Concept of KRANIOPHARYNGEOM 2007

3.1. Background
KRANIOPHARYNGEOM 2000 was the precursor prospective multicenter surveillance study to KRANIOPHARYNGEOM 2007 and was closed in October 2006 as planned. One-hundred and twenty (120) patients were recruited during the five years recruitment period. Viable analyses of the study aims were made possible due to the outstanding volume of both the data captured and the degree of data feedback.

HIT-ENDO and KRANIOPHARYNGEOM 2000
Based on the KRANIOPHARYNGEOM 2000 interim analysis (March 2006) as well as published results of collaborative studies in connection with HIT ENDO and KRANIOPHARYNGEOM 2000, the following conclusions can be made:

• Hypothalamic involvement resulting in radical surgical procedures and hypothalamic lesions are both clear predictors for severe impairment in postoperative functional capacities and QoL (H.L. Müller 2003).

• Patient QoL is seriously impaired in appr. 50% of craniopharyngioma cases due to hypothalamic obesity (H.L. Müller 2001).

• Patients with severe obesity presented reduced long-term functional capacities following multiple neurosurgical interventions in the course of treating the disease (H.L. Müller 2003).

• Considering the long-term consequences in cases of craniopharyngiomas with hypothalamic involvement, it appears that intended radial neurosurgery is not advisable.

• Event-free survival rates following incomplete primary resections were less than encouraging (EFS: 0.22±0.09; three years post-OP), meaning they frequently resulted in early progression of residual tumor remnants (H.L. Müller, Sörensen 2006).

• Investigations of risk factors regarding residual tumor progression and/or its biological growth behaviour following primarily incomplete resection do not yet exist.

• With regard to the timing of postoperative irradiation after incomplete resection, there is an ongoing controversy over
to what extent does immediate postoperative irradiation help avoid residual tumor progression, repeated surgical interventions, and a reduced QoL in those high-risk patients with hypothalamic involvement?

versus
the strategy to survey clinical and imaging monitoring of potential tumor progression, and perform progression-contingent neurosurgical intervention plus irradiation only when/if tumor progression is detected.

Patients with hypothalamic involvement should be classified as high risk patients regarding long-term consequences and impaired long-term prognosis based on the results of our interim analyses. There is consensus that complete resections are to be avoided for hypothalamic involved tumors based on the known, long-term consequences. In the interest of improving the QoL prognosis for these patients, studies are needed to provide scientifically-based recommendations regarding the appropriate therapy strategy(ies) following incomplete resections.
Literature
The value of postoperative irradiation of residual tumor remnants is unclear and inconsistently perceived by clinicians. An immediate postoperative irradiation is favoured by some in order to prevent possibly life-threatening situations due to possible future tumor progression (Thompson 2005). Arguing against this strategy is the cautious approach, postponing irradiation in order to reduce the consequences of unnecessary radiation therapy. That said, it is statistically undeniable that immediate postoperative irradiation significantly delays progression (Stripp 2004). As irradiation has no effect on total survival, it would appear that radiation therapy for relapse cases is highly effective (Stripp 2004). Three more recent series retrospectively compared immediate postoperative irradiation with irradiation at the time of relapse/progression in terms of effectiveness (Stripp 2004; Tomita 2005 and Moon 2005 – see table in Section 2.9, p. 19). No statistical difference was indicated with respect to overall survival in any of the three studies.

No differences in progression-free survival rates were found when comparing immediate irradiation vs. progression-contingent irradiation vis-à-vis relapses in the Moon study. However, tumor progression-contingent irradiation was associated with a clearly higher, negative influence on QoL, which is why the authors favour immediate irradiation (Moon 2005). It has to be mentioned that in this study, QoL parameters were restricted to ophthalmologic conditions and osmolality imbalances treated with DDAVP medication.

In the series reported by Tomita, relapse-free survival rates were 83% after 5 years and 70% after 10 years. The corresponding numbers for patients after incomplete resection plus immediate irradiation were 71 and 36% respectively. The 5 year relapse-free survival rate after incomplete resections without radiation therapy was only 9% (significantly statistically inferior to immediate irradiation). Relapse-contingent irradiation appeared highly effective as overall- and progression-free survival (PFS) rates were 90 and 70% respectively.

The literature regarding PFS following incomplete resection reflects the controversy between advocates of immediate radiation treatment directly after incomplete resections vs. proponents of a wait-and-see monitoring strategy using progression-contingent irradiation. Due to the lack of prospective, randomized data, no scientifically-based recommendation regarding optimal timing of postsurgical irradiation in cases of incomplete resection can be made at this time.

In KRANIOPHARYNGEOM 2000 no recommended strategy regarding irradiation after incomplete resection was made. Controversial concepts are reflected in the alternative treatment possibilities (H.L. Müller 2006): immediate local irradiation with 54 Gy frequency-doubled (ICRU 50) (ED 1.8 Gy, 5x / week) versus the what-and-see strategy using regularly-scheduled MRI monitoring in concert with progression-contingent irradiation.

Stratified randomization in KRANIOPHARYNGEOM 2007
A stratified randomization in two possible treatment arms (see p. 8) regarding timing of postoperative irradiation will be conducted for patients ≥5 years of age after incomplete resection in primary surgery. The randomization is performed three months after surgery. The randomization (3 mo after surgery) will be performed in a stratified manner, based on compiled PEDQOL scores at that time (60-90 days after surgery) regarding physical function. The stratification will performed for two separate groups according to baseline-QoL as measured 60 to 90 days after surgery (low PEDQOL randomization group = PEDQOL "physical functions" domain ≤56 points; high PEDQOL randomization group = PEDQOL "physical functions" = ≥56 points). The randomization will be performed in each distinct group (low / high PEDQOL baseline results 60 – 90 days after surgery) 3 months after surgery. The final analysis (3 years after randomization) will assess the main goal QoL (PEDQOL domain: physical function) and the subgoals of progression-free survival (EFS) and overall survival (OS). Changes between endpoint QoL and baseline QoL will be analyzed in relation to different timing schedules for irradiation of residual tumor (immediate postoperative irradiation versus MRI monitoring + progression-contingent irradiation of residual tumor [≥25%]).

Study endpoint
The duration of the study is subdivided into a phase running up until the interim analysis (IA), and the recruitment phase following IA – running up until the end analysis (EA). The IA is carried out after recruitment of 20 randomized patients and an observation of over three years (endpoint: PEDQOL physical function analysis three years after randomization). Based on the recruitment numbers of the precursor study (KRANIOPHARYNGEOM 2000), the Interim Analysis will probably begin ca. 5.5 years after study initiation (duration of IA data analysis is ca. ½ year).
After appr. 6-year study duration, the following scenarios are possible:

- If the IA phase indicates an early therapy effect (i.e. 5.5 years after study initiation), IA recruitment would be discontinued, yielding a total recruitment duration of 6 years. Patients recruited in years 2.5–4 would be treated as so-called interim patients with the assumption that, they being so far behind randomization initiation, it would no longer be possible to adapt their therapy to new IA insights. This means that the standard KRANIOPHARYNGEOM 2007 therapy treatment is allocated through randomization. For ethical reasons, one is still obligated to take into account any EA data for patients not included in the randomization. If QoL data for these patients is available 3 years after randomization, end analysis will still be conducted. EA begins ca. 7 years after study initiation; EA duration: ½ year. In this scenario, study endpoint would be ca. 7.5 years after study initiation.

- If the IA phase yields little or no therapy-effecting results, the study would be stopped at IA. In this scenario, earliest study endpoint would be ca. 6 years after study initiation.

- If the IA phase yields a moderate therapy effect, the recruitment period would be extended following IA somewhere around 4 years to a maximum of 6.5 years. Total recruitment duration from year-0 to year-10 would be extended to a maximum of 12.5 years. A follow-up period of 3 years would then ensue. In this scenario, study endpoint would be ca. 13 years with a maximum of 15.5 years after study initiation.

Considering the lengthy period of this study, changes and advancements in surgical and/or radiooncoloy therapeutic treatment can not be ruled out as having an effect on the EA (end analysis) phase, knowing that any advancement immediately effects treatment quality of both treatment arms within the context of randomization.

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<td>variable EA duration (depends on IA results and recruitment duration)</td>
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**Collaborative studies**

As was KRANIOPHARYNGEOM 2000, KRANIOPHARYNGEOM 2007 is open to collaborative studies in the interest of multicenter, interdisciplinary participation and cooperation. Material and data are made available with approval of the study commission to colleagues participating KRANIOPHARYNGEOM 2007. With regard to collaborative molecular genetic investigations, tumor material will be available for molecular studies (see section on Collaborative studies, p. 108).

**Patients studied in KRANIOPHARYNGEOM 2007**

For all other (non-randomized) patients (patients after complete resection and patients <5 years of age at the time of surgery regardless of the degree of resection), it is understood that this current investigation is a prospective, multicenter surveillance study that assesses the prognosis of craniopharyngioma patients in the context of the various currently-practiced therapy strategies. Data assessment is carried out in a standardized manner according to SIOP brain tumor groups. The international standardization of data capture with respect to diagnostics, therapy and prognosis of children and adolescents with craniopharyngioma was put in place to help increase the international cohort sizes, and in so doing, facilitate common SIOP data evaluation. The goal of the study is also to create a quality standard by examining the differences between the various therapy treatments with respect to their effectiveness and impact on the QoL of treated patients.
3.2. Study goals

Primary study aims

- Randomized investigation of changes in QoL of children (≥ 5 years of age) and adolescents following incomplete craniopharyngioma resections at primary diagnosis per QoL scores (PEDQOL "physical functions" domain) as measured 60-90 days after surgery and 3 years after randomization; and progression-free and overall survival rates (subgoal assessments) relative to how these parameters relate to postoperative irradiation timing (immediate postsurgery irradiation versus wait-and-see approach + progression-contingent irradiation of residual tumor).

- Compilation of applied therapy strategies for craniopharyngiomas in children and adolescents using data capture conforming to SIOP brain tumor groups

- Evaluation of patients' remission status following the various therapy strategies/modalities for craniopharyngiomas using data detection consistent with SIOP brain tumor groups

- Evaluation of the health status (ophthalmologic, neuropsychologic and endocrine conditions) and health-related QoL of children and adolescents following treatment of craniopharyngiomas using data capture conforming to SIOP brain tumor groups

Secondary study aims

- Investigation of frequency / incidence of craniopharyngiomas in children and adolescents

- Quality control of diagnostic and therapeutic modalities and procedures in patients with childhood craniopharyngioma

- Improvement of long-term care through a standardized follow-up treatment program

- Evaluation of endocrine substitution therapy for postoperative (pan-) hypopituitarism

- Prospective analysis of risk factors for the development of severe obesity

- Biological material / tumor banking (tissues, cerebrospinal fluids, cystic fluids, serum samples)

- Investigation of frequency of pituitary adenomas and menigiomas in children and adolescents in context of the HIT ENDO study (registry)

- Investigation of frequency of sellar and parasellar cystic deformities (arachnoid cysts and Rathke’s pouch cysts) in children and adolescents (registry)

- Investigation of frequency, treatment and prognosis of xanthogranulomas in children and adolescents
3.3. Patient admission

Criteria for admission

All patients meeting the following criteria will be admitted to KRANIOPHARYNGEOM 2007 as study patients:

1. Diagnosed with craniopharyngioma for the first time
2. Age at diagnosis ≤ 18 years of age
3. Agreement from patient’s parents or legal guardian as well as the patient

Criteria for inclusion in randomization study

1. Histological diagnosis of craniopharyngioma
2. Age at diagnosis ≤ 18 years of age
3. Age at primary surgery ≥ 5 years of age
4. Incomplete primary resection
5. Reference radiological confirmation of an incomplete resection
6. Agreement from patient’s parents or legal guardian as well as the patient

Non brain tumor patients

Patients with pituitary adenoma or meningioma will be reported to the German Pediatric Cancer Registry (DKKR). The DKKR will transfer the data to the study headquarter in Oldenburg. Data regarding frequency and incidence will continue the registration of these patients in the context of a 2001-initiated pilot study (see explanation and agreement clarification forms in supplemental information).

Patients with sellar/parasellar cystic deformities (Rathke’s pouch cysts, suprasellar cysts, etc.) as well as patients with xanthogranuloma will be reported and tracked by KRANIOPHARYNGEOM 2007 in a special registry.

The application form (p. 153) is available in all centers. It is the same for all tumors and after completion is to be sent to the German Pediatric Cancer Registry at the Institute for Medical Biometrics, Epidemiology and Medical Informatics, University Hospital Mainz. From there, the primary craniopharyngioma assessment forms will be sent to the recruiting center (see pp. 155–159, 163).

Data regarding the frequency and epidemiology of malignant and benign brain tumors is compiled and assessed in collaboration with the DKKR German Pediatric Cancer Registry (IMBEI at University Mainz; Prof. Dr. Blettner, Dr. P. Kaatsch).

Other brain tumor patients

A patient whose imaging indicated a suspected craniopharyngioma but was histologically excluded as such should be referred, along with their corresponding pathological findings, to the respective study responsible (HIT-MED 2000, SIOP-LGG, HIT-HGG, SIOP CNS GCT ’96, and LCH-III).
3.4. Statistical methods and design of the randomized study
Dipl. Math. oec. A. Emser, Prof. Dr. A. Faldum, IMBEI, University of Mainz

3.4.1. Design of the randomized study

The goal of the randomized study is to compare QoL of patients whose residual tumor was irradiated immediately following primarily incomplete resection with QoL of those whose residual tumor was not irradiated immediately following primarily incomplete resection. These KRANIOPHARYNGEOM 2007 incomplete resection patients are randomized into one of the two above-described treatment arms. The inclusion/exclusion criteria for the randomized study are:

**Inclusion criteria**
1. Histological diagnosis of the craniopharyngioma
2. Age at diagnosis ≤ 18 years of age
3. Age at primary surgery ≥ 5 years of age
4. Incomplete primary resection
5. Reference radiological confirmation of an incomplete resection
6. Agreement from patient’s parents or legal guardian as well as the patient

**Exclusion criteria**
No QoL measurement for randomization (3 months after surgery, 60–90 days).

This study is multicenter, non-blind, randomized and prospective. The study design is two-stage adaptive: Interim analysis will commence once the 3 y QoL of 20 study patients has been assessed. Based on the results of the interim analysis, the case numbers will then be determined for the second stage. This means that the recruitment window is determined by the results of the interim analysis of the 20 randomized patients, linking the recruitment window to the 3 y observation phase. Randomization will be stratified according to QoL scores taken 3rd month (60–90 days) post surgery. QoL will be rated according to patient-estimated PEDQOL “physical functions” domain scores (QoL_{Rand, P,D1}: ≤ 56 vs. > 56). The required randomization listings are available from the Institute for Medical Biometrics, Epidemiology and Medical Informatics at the University Hospital in Mainz.

The study adheres to principles of good clinical practice (GCP) defined by the ICH as well as the World Medical Association Declaration of Helsinki.

3.4.2. Goal assessments

Corresponding to the various study aims, the endpoints are defined as follows:

Patient QoL is measured by PEDQOL questionnaire ratings made at the following intervals:
- 3rd month (60–90 days) after surgery
- annually 5 years after randomization including 3rd year after randomization

At the above mentioned time points, patients (with parental support when necessary) and the parents will be asked to complete the PEDQOL questionnaire. The PEDQOL questionnaire consists of 7 domains:

**Main goal assessment**

1. The main goal assessment is based on changes in patient-rated QoL “physical functions” D1 domain scores made 3 months following surgery compared to scores made 3 years after randomization: Diff-QoL_{3, P,D1} = “QoL 3 years following randomization” minus “QoL 3 months following surgery according to self estimations of D1 domain”. For patients who die within the first 3 years after randomization, the equation is: Diff-QoL_{3, P,D1} = 2000 – number of days from randomization to patient death for any reason.

Because QoL scores range between 25 and 100 and decrease QoL-improved scores, Diff-QoL_{3, P,D1} can decrease scores from −75 to 75 for patients who do not die within the first 3 years after randomization, meaning QoL with positive differences worsens as time goes on. For patients who die within the first 3 years, Diff-QoL_{3, P,D1} ranges between 904 and 2000. In other words, Diff-QoL_{3, P,D1} decreases as lifespan increases.
Subgoal assessment

2.–7. Changes in patient QoL from 3 months postsurgery to 3 years after randomization according to self-estimations for D2–D7 domains (Diff-QoL\_3,\_P,D2, Diff-QoL\_3,\_P,D3, Diff-QoL\_3,\_P,D4, Diff-QoL\_3,\_P,D5, Diff-QoL\_3,\_P,D6, Diff-QoL\_3,\_P,D7). For those patients who die within 3 years after randomization, the equation is Diff-QoL\_3,\_P,D = 2000 – number of days from randomization to patient death for any reason. Because the QoL scores range between 0 and 100 and decrease QoL-improved scores, Diff-QoL\_3,\_P,D can decrease scores from –100 to 100 for patients who do not die within the first 3 years after randomization, meaning QoL with positive differences worsens as time goes on. For patients who die within the first 3 years, Diff-QoL\_3,\_P,D ranges between 904 and 2000. This means that Diff-QoL\_3,\_P,D decreases as lifespan increases.

8.–14. Changes in patient QoL from 3 months postsurgery to 3 years after randomization according to parent estimations for D1–D7 domains (Diff-QoL\_3,\_E,D1, Diff-QoL\_3,\_E,D2, Diff-QoL\_3,\_E,D3, Diff-QoL\_3,\_E,D4, Diff-QoL\_3,\_E,D5, Diff-QoL\_3,\_E,D6, Diff-QoL\_3,\_E,D7). For those patients who die within 3 years after randomization, the equation is Diff-QoL\_3,\_E,D = 2000 – number of days from randomization to patient death for any reason. Because the QoL scores range between 0 and 100 and decrease QoL-improved scores, Diff-QoL\_3,\_E,D can decrease scores between –100 to 100 for patients who within the first 3 years after randomization do not die, meaning QoL with positive differences worsens as time goes on. For patients who die within the first 3 years, Diff-QoL\_3,\_E,D ranges between 904 and 2000. This means that Diff-QoL\_3,\_E,D decreases as lifespan increases.

15. Progression-free survival rate (PFS) definition: time from date of randomization to appearance of tumor progression, death for any reason, or last follow-up examination without progression.

Tumor progression definition: see section 7.4. “Definition of resection and tumor response”.

16. Overall-survival rate (OS) definition: “Time from date of randomization to death for any reason or last follow-up examination of surviving patient.

Study patients will be assessed using the following neuropsychological tests at date of randomization and annually afterwards. Test executions are referenced in the glossary and in the respective study protocol sections.

17. FMH (German-developed functional abilities assessment questionnaire): tested annually
18. Kaufman-Assessment Battery for Children [K-ABC]: tested annually
19. Coloured Progressive Matrices Test [CPM]: tested annually
20. Hamburg-Wechsler intelligence children test [HAWIK VII] and H-W intelligence adult test [WIE]: tested annually
21. Bayley Scales of Infant and Toddler Development [BSID III]: tested annually
22. Developmental Test of Visual-Motor Integration [VMI]: tested annually
23. Conners’ Continuous Performance Test [CPT]: tested annually
25. Strength and Difficulties questionnaire [SDQ]: tested annually

Ophthalmological results

26. Vision acuity: tested annually
27. Field of visual test [Goldman perimeter] restricted? (no, yes); bitemporal hemianopsia (no, yes)
28. Fundoscopy [optic disc atrophy]: (no, yes)
29. Strabismus: (no, yes)
30. Body-Mass-Index SDS [BMI-SDS]
31. Height-SDS
32. Target Height (TH) related height-SDS

Hormone disturbances

33. Growth hormone deficiency (no, yes)
34. Hypothyroidism (no, yes)
35. Hypocortisolism (no, yes)
36. Diabetes Insipidus (no, yes)
37. Hypogonadism (no, yes)
38. Age at onset of puberty: (years-of-age) (see Glossary)
39. Onset of puberty: (definition – see Glossary)
   - absent/delayed puberty development
   - non-delayed puberty development

40. Hormone substitution therapy
   - recombinant human growth hormone (rhGH) (no, yes)
   - DDAVP (no, yes)
   - hydrocortisone (no, yes)
   - L-thyroxine (no, yes)
   - Sex steroids (no, yes)

41. Partial facial paralysis (no, yes) (definition: central nervous system-conditional paralysis)

42. Convulsion disorder: (no, yes) (independent of frequency and intensity of convulsion activity)

43. Headaches: (no, yes)

44. Anticonvulsion medication therapy: (no, yes)

Characteristic clinical symptoms of a hypothalamic syndrome

45. Eating disorders: (no, yes) (see Glossary)

46. Hypersomnia: (no, yes) (definition of daytime sleepiness = Epworth Sleeping Scale [ESS] score > 10)

Circadian rhythm disturbances

47. Daytime sleepiness: no/yes (definition of daytime sleepiness = Epworth Sleeping Scale [ESS] score > 10)

48. Nighttime sleep disturbances: no, yes (nighttime sleep disturbances = difficulties falling or staying asleep)

49. Temperature fluctuations: no, yes (definition of temperature fluctuations cannot be quantified without substantial research effort; subjectively stated = subnormal temperature < 36.5°C)

50. Prescriptive use of central stimulants: no, yes (definition: doctor-prescribed Methylphenidat or Modafinil)

51. Prescriptive use of psychopharmacaons: no, yes (definition: doctor-prescribed antidepressants)

Subgoal assessment – comparison of both treatment arms before randomization:

52. Intended degrees of resection at primary surgery:
   a) Radical, i.e. complete tumor resection
   b) Tumor volume reduction = incomplete resection (definition: see section 7.4. Definition of resection)
   c) Tissue sample biopsy: surgical intervention to remove tumor sample for histological diagnosis without intention of reducing tumor volume
   d) No surgery

53. Surgical access approach: (right front temporal, transspenoidal approach, other access approaches)

54. Surgical complications:
   - Haemorrhage: no, yes
   - Amaurosis fugax: no, yes
   - Apoplexy: no, yes

55. Perioperative complications:
   - Haemorrhage: no, yes
   - Infection: no, yes
   - Addison crisis: no, yes
   - Derailment of osmolality regulation: no, yes
   - Apoplexy: no, yes
   - Amaurosis fugax: no, yes
   - Other: no, yes

56. Tumor size: (tested annually) (definition: see section 7.4.)

57. Hypothalamus involvement
   - anterior hypothalamus: (no, yes). (anatomically defined and histologically evaluated by the radiology reference center – see Study Protocol)
   - posterior hypothalamus: (no, yes). (anatomically defined and histologically evaluated by the radiology reference center – see Study Protocol)

58. Imaging-revealed cystic component(s): (no, yes) (see Study Protocol)

59. Size of imaging-revealed cystic component(s): (tested annually) (see Glossary)
60. Imaging-revealed cystic component(s) of postoperative residual tumor: (no, yes) (see Glossary and Study Protocol)

61. Size of imaging-revealed cystic component(s) of postoperative residual tumor: (tested annually [cm³]) (see Glossary and Study Protocol)

62. Existence of tumor calcifications: (no, yes) (see Glossary and Study Protocol)

63. Size of postoperative residual tumor (tested annually [cm³]), (definition: see Glossary)

64. Localization of residual tumor (intrasellar, suprasellar, intra/ suprasellar) (definition: see Glossary)

65. CT scan-revealed existence of calcified components of postoperative residual tumor: no, yes (definition: see Study Protocol)

66. Degree of obesity:
   - Normal weight: BMI-SDS < +2SD
   - Moderately obese / overweight: BMI 2–3 SD
   - Obese BMI 3–7 SD
   - Severely obese BMI > 7 SD

67. Birth weight (gestational age at birth and gender-specific birth weight SDS): (weight recorded annually) (definition: see Glossary)

3.4.3 Study interrogations

This study is expected to answer the following questions.

Main study interrogation

1. What are the differences between the two treatment arms (see Study Design Flowchart, p. 8) in patient QoL changes from 3 months postoperatively to 3 years after randomization using patient-rated "physical function" domain D1 scores (Diff-QoL₃,P,D1)?

Ancillary study interrogations

2–14. Tracking the two postoperative treatment arms, what are the differences in patient QoL changes from 3 months postoperatively to 3 years after randomization in:
   - patient-rated D2 through D7 domain scores (Diff-QoL₃,P,D2 to Diff-QoL₃,P,D7)?
   - parent-rated D1 through D7 domain scores (Diff-QoL₃,E,D1 to Diff-QoL₃,E,D7)?

15–16. Tracking the two postoperative treatment arms, what are the differences in:
   - progression-free survival (PFS) rates?
   - overall survival (OS) rates?

17. –25. Tracking the test results of the two postoperative treatment arms, what are the different patient-rated score results of:
   - neuropsychological investigations (functional abilities assessment questionnaire [FMH], Kaufman-Assessment Battery for Children [K-ABC], Coloured Progressive Matrices Test [CPM], Hamburg-Wechsler intelligence children test [HAWIK IV], Hamburg-Wechsler intelligence adults test [WIE], developmental test of Visual-Motor Integration [VMI], Conners’ Continuous Performance Test [CPT], Bayley Scales of Infant and Toddler Development [BSID III], Child Behaviour Checklist [CBCL/4-18] up until 3 years after randomization initiation?
   - other tests (HIT-Leben), the health-related QoL using the Strength and Difficulties Questionnaire [SDQ] up until 3 years after randomization initiation?

26. –30. Tracking the different patient ophthalmologic results of the two postoperative treatment arms, what are the different scores for vision tests (field of visual test [Goldman perimeter]: restricted visual field? (no, yes), bitemporal hemianopsia (no, yes), fundoscopy [optic disc atrophy] (no, yes), and strabismus: (no, yes) up until 3 years after randomization initiation?

30. –32. Tracking the two postoperative treatment arms, what are the differences in obesity (body mass index SDS [BMI-SDS] up until 3 years after randomization initiation? Are there gender-related differences between the two treatment arms?

33. –38. Tracking the two treatment arms, what are the differences relative to:
   - short-term patient’s weight development (delta: [BMI-SDS 3 years after randomization] – [BMI-SDS at diagnosis])?
   - postoperative patient weight 1 year after surgery (delta: [BMI-SDS 1 year after diagnosis] – [BMI-SDS at diagnosis])?
   Are there gender-related differences between the two treatment arms?

39. –50. Tracking the two treatment arms, what are the measured differences relative to:
   - height-SDS up until 3 years after randomization initiation?
   - Target height (TH) related height-SDS up until 3 years after randomization initiation?
   - growth rates (delta: [height-SDS 3 years after diagnosis] – [height-SDS at diagnosis])?
Target height (TH) related growth rates (delta: [TH-height-SDS 3 years after diagnosis] – [TH-height-SDS at diagnosis])?

Are there gender-related differences between the two treatment arms?

51. –55. Tracking the two treatment arms, what are the presented differences relative to hormone deficiencies (growth hormones, hypothyroidism, hypocortisolism, diabetes Insipidus, and hypogonadism)?

56. –57. Tracking the two treatment arms, what are the measured differences relative to patient ages at onset of puberty, and are there higher rates in delayed puberty development?

58. –62. Tracking the two treatment arms, what are the differences in patients regarding hormone substitution therapy (recombinant human growth hormone (rhGH), DDAVP, hydrocortisone, L-thyroxin, or sex steroids)?

63. –65. Tracking the two treatment arms, what are the differences in patients regarding neurological status (paralysis, convulsion disorder, and/or headaches)?

66. Tracking the two treatment arms, what are the differences in patients regarding anticonvulsion medication therapy?

67. –81. Tracking the two treatment arms, what are the measured differences relative to observable clinical symptoms of hypothalamic disturbance syndromes (eating disorders, hypersomnia, circadian rhythm disturbances [daytime sleepiness, nighttime sleep disturbances], and temperature fluctuations)? Are there gender-related differences between the two treatment arms?

82. –83. Tracking the two treatment arms, what are the differences in patients regarding:
- prescriptive use of central stimulants?
- prescriptive use of psychopharmacons?

84. –86. Are there differences in the two treatment arms regarding:
- hospital-provided or out-patient rehabilitation provisions?
- hospital-provided or out-patient psychotherapy provisions?
- frequency of out-patient physician-provided follow-up care?

Investigation questions regarding homogeneity of the two treatment arms before randomization

87. –103. Are there differences in the two treatment arms regarding:
- primary intended surgical resections grades?
- surgical tumor access approaches?
- primary surgical measures with the intention to relieve intracranial pressure (cerebrospinal fluid shunts)?
- surgical complications?
- perioperative complications?
- presurgery tumor sizes?
- presurgery tumor localizations (intracellar, suprasellar, intra/ suprasellar)?
- hypothalamic involvement (anterior, posterior) in the preoperative imaging?
- indications of cystic components in the preoperative imaging?
- size of cystic components in the preoperative imaging?
- indications of tumor calcifications in the computerized tomography (CT)?
- size of postoperative residual tumor?
- postoperative localization of residual tumor (intracellar, suprasellar, intra/ suprasellar) in the postoperative imaging?
- hypothalamic involvement (anterior, posterior) of residual tumor in the postoperative imaging?
- cystic components in imaging of postoperative residual tumor?
- size of cystic components in postoperative residual tumor?
- indications of calcified components in postoperative residual tumor in postoperative computerized tomography (CT)?

104. –107. Are there differences in the two treatment arms regarding:
- the degree of obesity in the biological father (BMI SDS of father at craniopharyngioma diagnosis)?
- the degree of obesity in the biological mother (BMI SDS of mother at craniopharyngioma diagnosis)?
- gestational age at birth of patients (pregnancy duration [weeks])?
- birth weights of patients (gestation age- and gender-specific birth weights-SDS)?
3.4.4. Statistical analysis

Study analyses are to be carried out at the Institute for Medical Biometrics, Epidemiology and Medical Informatics at the University Hospital in Mainz utilizing the statistical software SPSS. The confirmatory analyses will be processed according to the intention-to-treat-principle. An explorative per-protocol-analysis and an as-treated-analysis will also be performed.

Per Protocol patients are defined as:

All patients treated with the therapy allocated to them according to the randomization process qualify as per-protocol patients.

Protocol deviations apply to both protocol treatments – Treatment Arm I with immediate postoperative irradiation and Treatment Arm II with irradiation following progression of residual tumor:

- Deviation from a cumulative end dose of +/- 10% (+/- 5.5 Gy)
- Deviation from a per single dose of +/- 0.18 Gy
- Deviation from a planned total treatment period of more than 3 weeks
- Deviation from the target volume concept

In addition, for patients treated per Treatment Arm II (wait-and-see following surgery, progression-contingent irradiation), any initiation of irradiation (with a dispensed cumulative irradiation dose greater than 5.5 Gy) without progression of residual tumor will be considered a deviation from protocol.

As-treated patients are defined as:

All patients who received either of the treatment arm therapies (with or without immediate irradiation) independent of randomization findings and without adherence to therapy deviations are classified as as-treated patients.

The analyses of the main study question (p. 41) will be analyzed in the intention-to-treat patient population bilaterally using a significance level of 0.05. The p-values relative to the answers to the ancillary study interrogations as well as to the per-protocol and as-treated patient analyses will be considered explorative. The total number of executed tests will be cited in the publication of ancillary study interrogations results.

Missing values

For the survival rate analyses, missing values will be treated as censored data. The remaining patient cases with complete datasets will be evaluated in the primary analysis. As a subsequent step, sensitivity analyses will be carried out for cases with missing values, replacing missing QoL values with the individual preceeding QoL values. The results of these sensitivity analyses will be discussed in the final report.

Null hypothesis and statistical tests

Main study interrogation

1. Null hypothesis:
Changes in patients’ self-rated QoL scores for the "physical function"domain (Diff-QoL\textsubscript{3,P,D1}) taken 3 months postoperatively and annually up until 3 years after randomization do not differ for patients who had immediate primary postoperative irradiation after incomplete resection vs. patients who did not have immediate irradiation following their incomplete resection.

This hypothesis will be verified by two unilateral Mann-Whitney U tests of differences for unpaired random samples. To illustrate statistical results for both treatment arms, box plots of Diff-QoL\textsubscript{3,P,D1} relative to both treatment arms, the medians, 1\textsuperscript{st} and 3\textsuperscript{rd} quartiles, and minimum and maximum values for Diff-QoL\textsubscript{3,P,D1} will be depicted.

Ancillary study interrogations

The following ancillary study interrogations will be examined in the end analysis:

2. Null hypothesis:
Changes in QoL 3 months following surgery up until 3 years after randomization:

a. According to patient self-rated scores for D2 to D7 domains (Diff-QoL\textsubscript{3,P,D2} to Diff-QoL\textsubscript{3,P,D7})

b. According to parent-rated scores for D1 to D7 domains (Diff-QoL\textsubscript{3,EL,D1} to Diff-QoL\textsubscript{3,EL,D7})
for patients who were immediately irradiated after incomplete resection does not differ from that of patients who were not irradiated immediately after incomplete resections. These hypotheses are to be verified by two unilateral Mann-Whitney U tests of differences for unpaired random samples. To illustrate statistical results for both treatment arms, box plots of changes in QoL relative to both treatment arms, the medians, 1st and 3rd quartiles, and minimum and maximum value of QoL changes will be depicted.

15. Null hypothesis: The progression-free survival (PFS) rate of patients who were irradiated immediately after incomplete resection does not differ from that of patients who were not irradiated immediately after incomplete resections. This hypothesis will be checked for disparities using a bilateral log-rank test. To illustrate statistical results for both treatment arms, the Kaplan-Meier curves of the PFS, PFS quartile with 95% confidence intervals, and the 1 y, 3 y and 5 y PFS rates with accompanying 95% confidence intervals will be depicted.

16. Null hypothesis: The overall survival (OS) rate of patients who were immediately irradiated immediately after incomplete resection does not differ from that of patients who were not irradiated immediately after incomplete resections.

To illustrate statistical results for both treatment arms, the Kaplan-Meier curves of the OS, OS quartile with 95% confidence intervals, and the 1 y, 3 y and 5 y OS rates with accompanying 95% confidence intervals will be depicted.

17. Null hypothesis: Both treatment patient groups do not differ regarding ancillary study interrogations 17 to 107 vis-à-vis corresponding main- or subgoal assessment categories. These hypotheses, in instances of:

- a constant goal assessment category will be checked for disparities using bilateral Mann-Whitney U tests of two non-paired random samples.
  To illustrate statistical results for both treatment arms, box plots of the respective constant goal assessment category, medians, 1st and 3rd quartiles, and minimum and maximum value for the respective goal assessment categories will be depicted.

- a binary goal assessment category verified using a precision test according to Fisher.
  To illustrate statistical results for both binary goal assessment categories, the corresponding cross table will be depicted.

- a categorical target dimension (more than two effects) verified using the \( \chi^2 \)- independence test.
  To illustrate statistical results for each categorical target dimension (defined as having more than two effects), the corresponding contingency table will be depicted.

In addition to analyzing all hypotheses for the total cohort, these hypotheses will be applied to a part of the ancillary study interrogations (see Section 3.4.3, pp. 41–42) and investigated separately for female and male patients.

3.4.5. Interim-analysis and end-analysis

After having defined the main goal assessment (p. 38), only those patients who have the minimum 3 years of follow-up after randomization will be included in the interim analysis. If the study concludes after the interim analysis in accordance with the group sequential or adaptive standard design (see study end point definitions, pp. 34–35), the information would be lost for the confirmatory study analysis for those patients (i.e. interim patients) who were randomized in the 3 years previous to the interim analysis.

However, for study efficiency as well as ethical reasons, all available information must be considered in order to come to an integrugous study statement. It is for these reasons that an adaptive study design is in place so that all evaluable, randomized patients are considered in the confirmatory analysis (A. Faldum, G. Hommel: Strategies for including patients recruited during interim analysis of clinical trials, Journal of Biopharmaceutical Statistics, submitted). The selected parameters for this adaptive design are as follows:

- two-stage adaptive design
- significance level: 5%
- bilateral study interrogation: realization via two unilateral questions to 2.5% respectively
- balanced design in both steps: equal number of patients per treatment arm
- case load for first stage: 20 (10 per treatment arm)
- expected number of interim patients: 6 patients per treatment arm
- the null hypotheses of the main study interrogation will be verified as follows:
  - Should either one of the two unilateral interim analysis p-values be \( \leq 0.015 \), randomization will be stopped. The year following interim analysis then becomes the newly established main study interrogation point for all patients, analyzing those whose randomization has at least 3 years to go and who were not considered in the previous interim analysis (analysis of interim patients). This
analysis is unilateral in the direction of the lesser of the two interim analysis p-values. If the resulting p-value of this newly established unilateral analysis is ≤ 0.1473, the null hypothesis in the direction of the lesser of the two interim analysis p-values is rejected. Otherwise, the null hypothesis stands.

- Should either one of the two unilateral interim analysis p-values be > 0.015 and one of the two unilateral interim analysis p-values be ≤ 0.2, the 2nd-stage case load in the direction of the lesser of the two interim analysis p-values (p1) becomes the new case load amount (see 3.4.6) and randomization continues. The null hypothesis in the direction of p1 is rejected if the p-value of the end analysis (unilateral test in the direction of p1) is ≤ 0.0655 / (p1 + 0.4298). Otherwise, the null hypothesis stands.

- Should both unilateral interim analysis p-values be > 0.2, randomization will be cancelled and the null hypothesis stands. The decision to select 0.2 as the limit for a study end supports the null hypothesis because even in a 2nd-stage 10 year recruitment window, no contingent power of 75% is attainable (see Section 3.4.6).

Note in the above-mentioned study-end parameter decision that the unilateral p-values in the Mann-Whitney U-Tests cannot simultaneously be ≤ 0.2 in both directions.

3.4.6. Case load planning

Therapy effect estimation:
Therapy effect estimation is based on a study that had a relatively light case load. The study investigated 8 patients without irradiation and 3 patients with immediate irradiation regarding their postoperative 3rd month, 1-, 2-, and 3-y QoL. Because the follow-up QoL data were incomplete, the evaluation of average QoL change effects over the 3 years was skewed for all 11 patients. This necessitated a Mann-Whitney U-Test estimation: the probability being 0.25 that Diff-QoL\(_{3,P,D1}\) for the non immediately-irradiated patients is less than Diff-QoL\(_{3,P,D1}\) for patients immediately irradiated.

Recruitment rate estimation:
- Based on KRANIOPHARYNGEOM 2000 rates, the estimated annual recruitment rate for KRANIOPHARYNGEOM 2007 is 24 craniopharyngioma patients per year.
- From those patient numbers, roughly 50% diagnosed for more than 5 years will have had an incomplete resection. This means that 12 patients per year, whether they fulfill the resection grade criterion or not, will be included in the randomized investigation.
- It is estimated that 80% of patients will agree to participate in this randomized study. That means that 9 to 10 patients would be randomized per year.
- We extrapolate from these numbers that ca. 90% of randomized patients will be implementing of a QoL assessment 3 years following their primary surgery. Altogether we assume that data from 8 to 9 patients will be available for statistical analyses 3 years after each recruitment year.

Stage 1. analysis:
According to the Interim-Analysis and End-Analysis sections (see 3.4.5) defining adaptive design, 20 patients will be required for Stage 1. three years after the randomization QoL measurement. Therapy effects estimated > 0.25 render a 40.8% probability that the unilateral Stage 1. p-value favours a better QoL for an immediate irradiation rate that is < 0.015 (G. E. Noether: Sample size determination for some common nonparametric tests, Journal of the American Statistical Association, 1987, pp. 645–647). Therapy effects estimated > 0.25 renders an 86.3% probability that the unilateral Stage 1. p-value favours a better QoL for an immediate irradiation rate that is < 0.2 (G. E. Noether: Sample size determination for some common nonparametric tests, Journal of the American Statistical Association, 1987, pp. 645–647).

If the randomization rate turns out to be 9–10 study patients per year, and QoL measurements are initiated for 90% of the randomized study patients 3 years after randomization, the interim analysis can be implemented approximately 5 ½ years afterwards.

Number of interim patients:
Based on previous experience with analyzing pediatric oncology therapy optimization studies, the entire interim analysis (data acquisition, feasibility studies, and clarification of missing/doubtful data, database closure, and analysis) must be accomplished in the period of time starting appr. 6 months into the 3-year postoperative QoL inquiry of the 20th patient until their QoL inquiry ends 3 years later. Consequently, patients are randomized 6 years until the end of the interim analysis, but only patients of the first 2 ½ years following the initiation of the randomization study can be included in the interim analysis. If the interim analysis should show a clear, advantageous effect of one of the two treatment arms (a unilateral Stage 1. p-value ≤ 0.015), randomization is stopped. One can therefore assume that the therapy for patients randomized for a shorter period of time (those whose randomization
commenced towards the beginning of the randomization process) will be altered according to interim analysis results. That means that according to the 3.4.5. Interim-Analysis/End-Analysis specifications, planned analysis of interim patients only comes into question for those who were randomized for a longer period of time. If one assumes that patients with a minimum of 2 years randomization observation receive further protocol-appropriate treatment that needs to also apply to the post-randomization analysis of interim patients that became available 2½ to 4 years after the initiation of the randomization study. An annual randomization rate of 8–9 patients results in ca. 6 patients per treatment arm for interim patient analysis.

Stage 2. case load and power:
The Stage 2. case load will result from the interim analysis case load planning, meaning all Stage 1. internal and external information will be used for Stage 2. case load planning. The Stage 2. contingent power aim is 75%. Because the estimated Stage 1. therapy effect was based on an observation study with a low case load, planned Stage 2. case load shall be based on the Stage 1. therapy effect. The Stage 2. recruitment window (inclusive of Stage 2. three-and-a-half years remaining randomization) is not to exceed 10 years.

An annual randomization rate of 8–9 patients results in a maximum Stage 2. case load of 45 patients per treatment arm. The Stage 2. case load is linked to Stage 1. if-then p-values depicted in Graph 1 (see below). A restricted Stage 2. case load out of this 45 per therapy-arm maximum yields the contingent Stage 2. power values depicted in Graph 2 (see below). The above-described guidelines for case load planning are not obligatory and can be adapted to internal and external information after the interim analysis.

Graph 1: Stage 2. per treatment arm case load is linked to the lesser of the two unilateral Stage 1. p-values (p1) under the following conditions: Stage 2. Local significance level is 0.0655 / (p1 + 0.4298) when p1 is > 0.015. The Stage 2. test is unilateral. As a planning probability, if the Diff-QoL of non-immediately irradiated patients is < Diff-QoL of the patients with immediate irradiation, then the observed relative frequency in Stage 1. is selected. The conditional Stage 2. power is 75% (case load calculation is according to G. E. Noether: Sample size determination for some common nonparametric tests, Journal of the American Statistical Association, 1987, pp. 645–647). If p1 ≤ 0.015, then 6 interim patients will be analyzed for each Stage 2. treatment arm.

Graph 2: Conditional Stage 2. power is contingent upon the lesser of the two unilateral Stage 1. p-values (p1) under the following conditions: Stage 2. local significance level is 0.0655 / (p1 + 0.4298) when p1 is > 0.015. The Stage 2. test is unilateral. As a planning probability, if the Diff-QoL of non-immediately irradiated patients is Diff-QoL of the patients with immediate irradiation, then the observed relative frequency in Stage 1. is selected. The Stage 2. case load will be calculated so that a power value of 75% is maintained (Graph 1) as long as a 45 per treatment arm patient case load is not exceeded and p1 is > 0.015. If p1 ≤ 0.015, then 6 interim patients will be analyzed for each Stage 2. treatment arm.
3.4.7. Discontinuation of randomized study for safety reasons

After 2 and 4 years of recruitment, safety analyses will be carried out using log rank tests. Significance level for each analysis is 20%. Testing is not corrected for multiples because the focus here lies on identifying survival rates in both groups.

1. After 2\textsuperscript{nd} year safety analysis

<table>
<thead>
<tr>
<th>test</th>
<th>(\alpha)</th>
<th>uni/bilateral</th>
<th>effect: 2 year OS</th>
<th>safety-analysis case load</th>
<th>power</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20%</td>
<td>bilateral</td>
<td>95% vs. 90%</td>
<td>N = 20</td>
<td>16%</td>
</tr>
<tr>
<td>2</td>
<td>20%</td>
<td>bilateral</td>
<td>95% vs. 85%</td>
<td>N = 20</td>
<td>21%</td>
</tr>
<tr>
<td>3</td>
<td>20%</td>
<td>bilateral</td>
<td>95% vs. 80%</td>
<td>N = 20</td>
<td>26%</td>
</tr>
<tr>
<td>4</td>
<td>20%</td>
<td>bilateral</td>
<td>95% vs. 75%</td>
<td>N = 20</td>
<td>31%</td>
</tr>
<tr>
<td>5</td>
<td>20%</td>
<td>bilateral</td>
<td>95% vs. 70%</td>
<td>N = 20</td>
<td>35%</td>
</tr>
<tr>
<td>6</td>
<td>20%</td>
<td>bilateral</td>
<td>95% vs. 65%</td>
<td>N = 20</td>
<td>39%</td>
</tr>
</tbody>
</table>

The 2-year OS rate for patients with immediate irradiation is assessed at 95%.

With a significance level of 20% and a bilateral interrogation that assumes a distributed exponential survival, 10 patients annual recruitment rate, same case load for both treatment arms, can identify a reduction of the post 2-year OS rate of around 25% with a power of 35% in the first safety analysis and a post 4-year OS rate with a power of 69% in the second safety analysis.

A 2-year OS rate reduction of only 5% with a power of 16% can be identified in the first safety analysis and with a power of 24% in the second safety analysis.

Power is to be calculated \textsc{nquery} advisor 5.0. The safety analysis results will be discussed by the DMC (data monitoring committee) if one of either of the log rank tests shows a significant difference in survival rates of both treatment arms.

Kaplan-Meier curves for OS survival rates will also be sent to the DMC. There is also the possibility that the DMC recommends the study be stopped if only very meagre therapy effects are achieved.

3.5. Design and statistical methods of investigation of patients after complete resection and patients less than 5 years-of-age at the time of diagnosis

All patients not meeting admittance criteria for the randomized study will be admitted to the KRANIOPHARYNGEOM 2007 surveillance study when meeting the following criteria:

- Histological diagnosis of the craniopharyngioma
- Age at incomplete resection: < 5 years of age
- Age at complete resection: \(\leq\) 18 years of age
- Agreement from patient’s parents or legal guardian as well as the patient

Statistical analyses are performed by the HIT biometric reference center at the Institute for Medical Biometrics, Epidemiology and Medical Informatics at the University Hospital in Mainz (Dr. A. Faldum, Dipl. math. oec. A. Emser), University Hospital Mainz (IMBEI director: Prof. Dr. Blettner). Basically, all CNS tumor treatment admission forms are directly forwarded to the German Pediatric Cancer Registry (Dr. P. Kaatsch). From there, the assessment forms prepared by the applicable study administration are dispatched. This procedure has been an integral information exchange feature between pediatric oncology hospitals, study administrations and the German Pediatric Cancer Registry for many years and is practiced by other pediatric brain tumor studies. While total percentage of diseases captured by the German Pediatric Cancer Registry is generally about 95%, the rate is considerably lower for chemotherapy-treated CNS tumors, including craniopharyngiomas. The goal is to elevate this reporting rate to a height comparable with international data rates.

Study initiation: 01.October.2007

Recruitment phase: October 2007 – September 2012

Expected case load: Of approximately 24 patients per year with craniopharyngioma, half of them (<5 years-of-age or with a complete resection) will be included in the surveillance study (based on an annual occurrence rate of 0.5–2 / 10\(^6\) / persons, of which 30– 50% are children and adolescents – recruitment estimates drawn from KRANIOPHARYNGEOM 2000).
The Goal of KRANIOPHARYNGEOM 2007 for patients who do not meet the randomization criteria is a prospective assessment of effectiveness and compatibility of individually-selected therapy strategies based on the following parameters:

End points
- **Overall survival (OS)**: Criterion is time of death. No distinction is made whether the death is or is not associated with the disease.
- **Event-free survival (EFS)**: Occurrence of death, relapse, or progression of residual tumor.
- **QoL**: (Change in QoL from 3rd month post OP up until 3 years after OP): according to QoL parameters rated as percentile ranges from FMH-functional abilities scale and PEDQOL-scores.

Magnitude of influence
From examined influence of the following prognostic factors:
- Surgical treatment strategy (planned complete resection vs. incomplete resection plus immediate irradiation)
- Degree of resection (surgery reports, neuroradiology assessment)
- Tumor localization and extent (imaging)
- Executing and method of irradiation (Radiooncology Dept, University Leipzig)
- Degree of obesity (BMI SDS)
- Vision capabilities (ophthalmological findings)
- Developmental assessment in infants (BSID III)
- Intelligence deterioration (K-ABC, HAWIK IV, HAWIVA-III; CPM/SPM)
- Attention and concentration deficits (VMI)
- Behavioural syndromes (CBCL/4−18)

Objectives
- Achievement of scientifically-based therapy recommendations
- Standardization and quality control of diagnostics, therapy, and follow-up care

Subsequent investigation
The continued observation of patients is planned in context of a subsequent investigation following the recruitment phase process (2007−2012). The first evaluation is scheduled 24 month after the end of the recruitment phase (October 2014).

Criteria for protocol changes
New scientific insights in diagnostics and/or therapeutic modalities in craniopharyngioma will be communicated in writing to participating centers with approval of the study commission. Because of the surveillance nature of the study, such insights will not require protocol changes. Necessary changes or supplements to the study protocol must be approved by a study commission majority and must be distributed in writing to the participating centers by the study administration.

Criteria for study discontinuation
To preserve patient security, the following criteria are defined for discontinuing the study:
- Should a different, multicenter prospective and randomized study publish a significant, defined advancement in therapy modality regarding craniopharyngioma patient prognosis before the current study’s recruitment phase concludes, KRANIOPHARYNGEOM 2007 will be discontinued after consultation and decree by the study commission (simple majority) and immediately announced to the participating centers. The collected data will be archived by the study director Prof. Dr. med. H. Müller in case the study is discontinued.
Data monitoring
The study commission will name a data monitor in their first session. The data monitor will be excluded from membership in the study commissions.

Statistical methods of the surveillance study
Data analysis will be performed using a commercial statistics program (SPSS for Windows®, SPSS Inc.), supervised by the Institute for Medical Biometrics, Epidemiology and Medical Informatics at the University Hospital in Mainz (Dr. A. Faldum, Dipl math. oec. A. Emser). Standard descriptive statistical procedures will be used to generate hypotheses pertaining to testing this prospective follow-up study. The statistical analysis results will be performed 24 months after the recruitment phase ends (October 2014). An interim analysis of non-randomized patients is planned after a 3 year run time (October 2010).

Publication of study results
The study commission has decision-making authority over publication of results. The study results are to be published in every case, the modalities governed according to publication rules for therapy optimization studies set by the German Society of Pediatric Oncology and Hematology (GPOH – Gesellschaft für Pädiatrische Onkologie und Hämatologie).

3.5.1. Study directorship and supervision
The study will be conducted under the direction of Prof. Dr. med. H. Müller, Klinikum Oldenburg gGmbH, Germany. The makeup of the study commission reflects both the study’s multidisciplinary approach as well as its administration. The composition of the study commission is defined in this protocol (listing, p. 125).

Require material for study monitoring
- Original film or CDs of pre- and postoperative MRI/CT-imaging (returned ASAP after scanning/archiving). Copies of relevant radiological diagnostic imaging should be sent as an exception only.
- Copies of the radiological findings and surgery reports
- The Department of Radiation Therapy, University Leipzig should review the irradiation plan for all randomized patients (≥5 years-of-age following incomplete resection). The Radiation Therapy Technique form (Form 3, p. 158) should be sent directly to the study administration (fax: +49 (0)441-403-2789) for forwarding to the Department of Radiation Therapy, University Leipzig (Prof. Dr. Rolf Dieter Kortmann, Leipzig). A radiooncological therapy recommendation with explanatory comments will be promptly returned to participating clinics based on the submitted data (Form 3, p. 158).
- Assessments (see Forms 1−13, pp. 156−168)
- Documentation regarding maximum acute toxicity levels during and at end of irradiation (Forms 10 & 11, pp. 165−166)
- To extent available: intraoperatively acquired CSF sample, cystic fluid, and tumor tissue specimens (see p. 66 for shipping address)
- Copies of physician letters

The following will be assessed by reference-radiology:
- pre- and postoperative MRI imaging for all patients
- preoperative CT imaging (without contrast agent) for all patients
- postoperative, native CT monitoring of preoperatively-indicated calcification
- progress of residual tumors at imaging location for randomized patients in both treatment arms I and II
- Monitoring examinations of randomized patients following irradiation
3.5.2. Documentation

Documentation is oriented towards standardization efforts made by the KRANIOPHARYNGEOM 2000 and HIT studies. It consists of:

General treatment application forms: (pp. 153–154)
These forms are only available at the participating centers. Forms for all malignant diseases as well as for all CNS tumors (regardless of ranking) should immediately sent to the Institute for Medical Biometrics, Epidemiology and Medical Informatics at the University Hospital in Mainz. The craniopharyngioma assessment forms are then sent to the centers from Mainz.

Craniopharyngioma assessment forms: (pp. 155−159, 163)
Craniopharyngioma assessment forms (Forms 0−4, 8) will be sent from the German Pediatric Cancer Registry in Mainz to the treatment center, where they are to be filled out and then sent to the study’s administration (Klinikum Oldenburg gGmbH, Germany). They need to be specifically analyzed by the craniopharyngioma study and should include: patient age, preoperative symptom(s), symptom(s) duration, patient’s and their family anthropometric data, patient’s endocrine condition, primary tumor localization and size, surgical strategy (intended complete/incomplete resection), and size of any postoperative residual tumor remnant.

Of particular importance is the assessment of the degree of resection (complete versus incomplete resection) indicated by postoperative imaging (MRI + as-needed native CT) in preparation for patient randomization!

Data assessment forms

- Application form (pp. 153−154)
- Assessment Cover Sheet (Form 0, p. 155)
- Diagnosis Data (Form 1, includes disclosure of resection grade, p. 156)
- Surgery Process Data (Form 2, p. 157)
- Irradiation – Therapy Technique (Form 3, p. 158)
- Submission Form for Radiological Reference Assessment (Form 4, p. 159)
- Course Documentation – I (Form 5, p. 160)
- Course Documentation – II (status, relapse/progression, death – Form 6, p. 161)
- Radiological Reference Assessment (Form 7, p. 162)
- Parental Agreement and Randomization Request (Form 8, p. 163)
- Randomization Confirmation (Form 9, p. 164)
- Irradiation – Acute Toxicities (toxicity detection during irradiation – Form 10, p. 165)
- Irradiation – Acute Morbidities (toxicity detection at end of irradiation – Form 11, p. 166)
- Irradiation – Long-term Consequences (Form 12, p. 167)
- Notification of Undesirable Events (Form 13, p. 168)

Neuropsychological examinations should be performed preoperatively, 3 months postoperatively, and annually at a pediatric oncological treatment center. (p. 60)

Copies of physician letters regarding the usual patient care information should be sent to the study’s administration.

Reference histology: histology findings uncovered by the reference center investigation (Pathology Bonn, Germany; Prof. Dr. Pletsch) should be sent to the corresponding pathologist/ neuropathologist, applicable treatment clinic, and study headquarters (see section 6, p. 66).

Reference radiology: Original or CD-ROMs of CT and MRI images of the initial preoperative and postoperative examination should be sent to the neuroradiology reference center in Würzburg for study evaluation (Neuroradiology Dept, University Würzburg, Germany). Continuous imaging monitoring of suspected progressions in randomized patients should also be sent to the reference center in Würzburg for co-evaluation.
Sending preoperative MRI/CT images and postoperative MRI/CT monitoring images for reference assessment is obligatory.

Reference assessment images will be returned to the participating center via quick post or fax. New telematic technology should to be used if available.

**Archiving study documentation** is done by the study’s administration. Report data will be archived by the German Pediatric Cancer Registry.

### Security determinations (detection and judgment)

#### Adverse Events

Undesirable events (adverse and unexpected events or AE and UE) are any unfavourable or unintended surveillance-period indication (including abnormal laboratory findings) of an accident during treatment of disease or impairment that is in fact considered independent of a possible causal connection with the study treatment. An UE is feasible during irradiation and/or surgery, i.e. toxicities such as those defined in the lab parameter documentation (Forms 10, 11, and 12). All other AE and UE are documented on Form 13 (p. 168) according to the Common Terminology Criteria for Adverse Events (CTCAE). The CTCAE includes the following degree-of-severity classifications:

- **Mild** (symptoms easily tolerated and requiring no change in treatment procedure).
- **Moderate** (symptoms serious enough to limit patient’s efficacy and requiring one medical intervention).
- **Severe** (symptoms severe enough to restrict patient’s efficacy to the extent that he/she cannot pursue his/her ordinary activities and requiring one medical intervention).

Moderate (non serious) and severe (serious) are distinguishable undesirable events. Every undesirable event fulfilling any one of the following criteria during the patient’s study surveillance period is considered serious:

- leads to death
- is life-threatening
- requires or extends hospital stay
- leads to chronic or distinct handicaps
- leads to a congenital anomaly or birth defect

Unexpected, undesirable events are events that are not yet expected in connection with the therapies used in this study.

Any connection between an UE and study treatment will be assessed by the study’s administration and assigned one of the following categories:

- no connection
- possible connection
- more-than-possible connection
- probable connection

**Serious** and **unexpected** undesirable events are to be reported within 24 hours via fax (+49 (0)441-403-2789) to the study’s administration.
4. Preoperative diagnostics – primary diagnosis

4.1. Obligatory diagnostics – primary diagnosis

<table>
<thead>
<tr>
<th>OBLIGATORY</th>
<th>page</th>
<th>Question / parameters</th>
</tr>
</thead>
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<td>Clinical neurological findings</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>native MRI + gadolinium</td>
<td>54</td>
<td>tumor dimensions</td>
</tr>
<tr>
<td>native CT</td>
<td>53</td>
<td>calcifications</td>
</tr>
<tr>
<td>ophthalmologic findings</td>
<td>54</td>
<td>field of vision, vision acuity, papilloedema</td>
</tr>
<tr>
<td>anthropometric examination</td>
<td>52</td>
<td>height, weight, body-mass-index (BMI), Tanner pubertal stage</td>
</tr>
<tr>
<td>laboratory diagnostics</td>
<td>54</td>
<td>prolactin, α-fetoprotein, beta-HCG, fT4, TSH testing for central diabetes insipidus</td>
</tr>
</tbody>
</table>

4.2 Optional diagnostics – primary diagnosis

<table>
<thead>
<tr>
<th>OPTIONAL</th>
<th>page</th>
<th>Question / parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>endocrine testing</td>
<td>55</td>
<td>preoperative baseline evaluation</td>
</tr>
<tr>
<td>neuropsychological diagnostics</td>
<td>54</td>
<td>preoperative baseline evaluation</td>
</tr>
<tr>
<td>QoL (PEDQOL)</td>
<td>57</td>
<td>preoperative baseline evaluation</td>
</tr>
</tbody>
</table>

Objectives of preoperative diagnostics

- Imaging confirmation of diagnoses as well as differential diagnostic limits in regard to other sellar/parasellar masses, as well as description of tumor dimensions and confirmation of cysts and/or calcifications for surgical planning
- Diagnosis of existing preoperative endocrine deficits needing immediate hormone substitution treatment (diabetes insipidus, hypocortisolism, hypothyroidism)
- Ophthalmological assessment of vision acuity, field of vision and existence of papilloedema
- Baseline evaluation before therapy (anthropometry, neuropsychology and health-related QoL)

4.3. History

Preoperative information regarding patient gestation conditions and events as well as parental auxiological case histories should be compiled (Surgery Process Data, Form 2, p. 157).

4.4. Clinical findings/anthropometric data

a. Complete physical and neurological investigation
Assessment of the pubertal stage (Tanner, 1955).
Volume (ml) of both testicles using Prader’s orchiometer.

b. Anthropometric measurements
Height and weight (Diagnosis Data, Form 1, p. 156).

- Patient’s height should be measured standing using a stadiometer. Baby and infant length measurement (up to 2 years of age) is taken while baby/infant is lying. Final height/length value is averaged from three consecutive measurements.
4.5. Preoperative neuroradiology imaging

- Magnetic resonance imaging (MRI) of the skull before and after gadolinium enhancement
- CT (without enhancement) to verify calcifications

**Magnetic resonance imaging (MRI)**
Cerebral MRI with and without contrast enhancement is the preferred neuroradiology technology for childhood brain tumors. The following MRI sequences are proposed:

Before gadolinium enhancement injection:
- $T_1$-weighted sagittal and coronary images (max. 3–4 mm thick tumor layers)
- Proton-weighted and $T_2$-weighted axial images of the entire brain

After gadolinium enhancement:
- $T_1$-weighted images, coronal and sagittal, as taken in pre-contrast enhancement images
- $T_1$-weighted axial images as done for $T_2$

**Computerized tomography (CT) – OBLIGATORY!**
CT is specifically used to identify calcifications frequently found in craniopharyngiomas. Because calcifications are not represented in the MRI, identifying their existence and localization using CT is absolutely key to surgical access approach planning. Another essential use of CT is the differential diagnostic requirement to rule out diencephalic astrocytomas through calcification verification. For the reasons just described, preoperative CT verification of calcification localization is an obligatory diagnostic consideration.

Frequently, post-operative CT imaging is performed to exclude postsurgical complications. Such postoperative native, non-enhanced CT monitoring should be used to screen for residual tumor calcifications. If preoperative CT has definitively ruled out the existence of calcifications, postoperative CT can be waived. In case of preoperatively detected calcifications the post-operative CT is recommended. Early postoperative MRI examinations (within first 48 to 72 hours) are not required because craniopharyngioma does not represent an intracerebral tumor.

MRI with and without contrast agent is a recommended, suitable imaging technology for regular follow-up monitoring in patients with residual tumors. When MRI is not available, CT with and without contrast agent can be used on an exception basis for follow-up monitoring. However, the cumulative lens dosage in follow-up CT examinations needs to be paid close attention to.

**Note:** Original images (or CD-ROM + DICOM data without viewer) of the following examination series should, along with the local radiologist findings, be sent to the KRANIOPHARYNGEOM 2007 neuroradiology reference center (Neuroradiology Dept., Prof. Dr. Warmuth Metz, University Würzburg; Germany):
- Preoperative MRI and CT
- Postoperative MRI and CT if used (depends on preoperative calcification verification)

**Send pre- and postoperative images to:**

Prof. Dr. M. Warmuth-Metz  
Neuroradiology Dept, Julius Maximilians University Würzburg  
Josef-Schneider-Str. 11, D-97080 Würzburg, Germany (Director: Prof. Dr. L. Solymosi)  
Tel: +49 (0)931-201-34799; Fax: +49 (0)931-201-34803  
E-mail: hit@neuroradiologie.uni-wuerzburg.de

Patient name and examination date need to be legibly stated on images. Images will be returned as soon as possible following reference center scanning/documentation. Please include accompanying Submission Form (Form 4, p. 159) when sending imaging for radiology reference assessment.
The following neuroradiology reference center-defined assessment parameters will be provided by the neuroradiology reference center using the Radiology Reference Assessment (Form 7, p. 162) and sent back to the participating center:

- Tumor size: primary, residual, and relapse tumors will be measured three dimensionally. A three-dimensional volume approximation is calculated using the rotation ellipsoid formula \( a \times b \times c / 2 \). The same tumor volume measurement formula is used for measuring cystic and solid tumor elements. Because the tumor is usually irregularly shaped, the formula only provides an approximation. Both personnel and hardware requirements are lacking for an exact volumetric calculation at this point in time as the images would have to be digitally formatted, fed into a computer, and measured layer by layer. The volume approach calculation is reached by detecting the largest craniocaudal diameter, anterior-posterior and transversal dimensions, comparing calculations to the historic collective when possible (usually only one layer measured) as another volume calculation approach.

- Tumor localization and extent
- Tumor structure: cystic, solid parts, calcifications
- Postoperative residual tumor remnant
- Tumor progression (compared to baseline)
- Alteration(s) to adjacent brain structures
- Aneurismata
- Hydrocephalus
- Contrast agent used in MRI
- CNS defects

4.6. Preoperative ophthalmologic diagnostics

Visual acuity; retina, optic nerve and optic disk examination (papilledema evaluation, qualified in dioptre range); visual field examination (Goldman perimeter or computerized axial perimeter); ocular motility (cover test); plus the optional colour vision test (Ishiara- or Matsubaro plates) and collimated light-emitting target test.

4.7. Preoperative neuropsychological examinations

Preoperative neuropsychological diagnostics are recommended only when the patient is in good clinical condition (no signs of brain pressure, headaches, or reduced general condition) and surgery should not be delayed for preoperative neuropsychological examinations. Preoperative diagnostics give important baseline information for making prospective follow-up course decisions, but on a practical level they must be oriented to local treatment center capacities and resources. Neuropsychological examination instruments are referenced in section 5.6, p. 58.

4.8. Preoperative laboratory diagnostics (except endocrine diagnostics)

<table>
<thead>
<tr>
<th>Peripheral blood count</th>
<th>LDH, import/export capacities</th>
</tr>
</thead>
<tbody>
<tr>
<td>plasma coagulation</td>
<td>serum/urine osmolality</td>
</tr>
<tr>
<td>serum creatinine, uric acid</td>
<td>fasting blood sugar</td>
</tr>
<tr>
<td>transaminase, serum electrolytes</td>
<td>osmolality in urine (1st morning urine)</td>
</tr>
</tbody>
</table>
4.8.1. Preoperative endocrine diagnostics

- DDAVP test for diagnosis of central diabetes Insipidus (test guidelines, p. 122)
- serum prolactin, α₁-fetoprotein, and β-hCG measurements
- thyroid parameters: fT₄, TSH
- serum/salivary cortisol profile or free cortisol in 24h urine collection test

Central diabetes insipidus: Increased serum sodium concentrations along with increased serum osmolality in concert with reduced urine osmolality points to central diabetes insipidus. DI is indicated by failures in normal serum osmolality and the kidney’s ability to maintain normal urine concentrations (urine weight >1.020, urine osmolality > 750 mosm/kg H₂O and/or quotient urine- serum osmolality >2). The DDAVP test (p. 122) specifies and distinguishes differences between central and renalis diabetes insipidus when diabetes insipidus is suspected. DDAVP substitution (nasal sol., parenteral sol. – see section on Pharmaceutical treatments 7.5, p. 73) is recommended after diagnosis of central diabetes Insipidus.

Hypocortisolism: Every cranioopharyngioma patient is at risk of manifesting hypocortisolism preoperatively and at an even higher risk perioperatively. Even if preoperative lab tests have excluded hypocortisolism (normal findings in circadian rhythm serum/saliva and 24h urine collection cortisol tests), hydrocortisone substitution in stress dosage must be preoperatively administered (increase normal dose [10–15 mg/m² BSA/d] 3–4 times, i.e. 30–50 mg/m² BSA/d). Hydrocortisone substitution is not necessary when dexamethasone is administered perioperatively. When dexamethasone therapy is administered perioperatively, hydrocortisone substitution should be initiated postoperatively – guideline being 10th postoperative day at the latest.

Hypercortisolism: Indicates an ACTH-secreting pituitary adenoma (further functional diagnostic: dexamethasone suppression test).

Hyperprolactinemia: Extremely elevated basal serum prolactin levels (>250ug/l, >5000mU/l) indicate a prolactinoma. (TRH test protocol, p. 119). Slight serum prolactin elevations are thoroughly consistent with the presence of a craniopharyngioma.

Increased levels of α₁-fetoprotein and β-hCG in serum/CSF: Elevated levels of α₁-fetoprotein and β-hCG in serum and especially in CSF are evidences of a secreting germ cell tumor (further diagnostic and therapeutic procedures according to SIOP CNS-Germ Cell Tumor Study, study director: Dr. G. Calaminus, University Hospital Münster, tel: +49 (0)251-83-58060, fax: +49 (0)251-83-87874, Münster, Germany). Unambiguously increased tumor markers in the serum and/or CSF spare the patient from invasive surgery.

Hypothyroidism: In secondary hypothyroidism, peripheral thyroid hormones (free T₄) are lower or in the lower end of the standard range (basal secretion). TRH test: in secondary pituitary hypothyroidism. TSH release response diminishes or is even absent following TRH administration; a different reaction pattern is found in tertiary hypothalamic hypothyroidism (see test protocol, p. 119).

Growth hormone deficiency: Low serum concentrations of IGFBP-3 or IGF-I substantiate suspicion of a growth hormone deficiency. Further diagnostics (GH stimulation tests 6 months after surgery, p. 120) and substitution therapy are not necessary before surgery and should never delay surgery.

Growth hormone excess: Significant increases in serum concentrations of IGFBP-3 and/or IGF-I can suggest an excess of growth hormone caused by a rare GH-secreting pituitary adenoma. Further functional diagnostics are necessary: oral glucose tolerance test to check for a GH-suppression caused by increased blood glucose.
Hypogonadism: Reduced serum sex steroid concentrations (estrogen, testosterone) and/or the basal gonadotropine (LH, FSH) substantiate the suspicion of secondary or tertiary hypogonadism in pubescent and adult patients. Further preoperative diagnostics such as introduction of a substitution therapy are not necessary and should never delay surgery. In prepubertal patients, very low sex steroid and gonadotropine serum concentrations are physiological findings.
5. Postoperative diagnostics

5.1. Overview of obligatory diagnostics during followup

<table>
<thead>
<tr>
<th>Question / parameters</th>
<th>Instrument</th>
<th>Page</th>
<th>Timing</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>QoL (HIT-Leben)</td>
<td>PEDQOL</td>
<td>61</td>
<td>3rd Mo (60–90 d)</td>
<td>1 × / y</td>
</tr>
<tr>
<td>Clinical neurological findings</td>
<td>MRI + as- necessary CT</td>
<td>57</td>
<td>3rd M</td>
<td>3-6 Mo</td>
</tr>
<tr>
<td>Neuroradiological imaging</td>
<td>FoV, acuity, papilloedema</td>
<td>58</td>
<td>3rd M</td>
<td>1 × / y</td>
</tr>
<tr>
<td>Anthropometric examination</td>
<td>endocrinology</td>
<td>64</td>
<td>6th M</td>
<td>1 × / y</td>
</tr>
<tr>
<td>Functional capacity</td>
<td>FMH</td>
<td>129</td>
<td>3rd M</td>
<td>1 × / y</td>
</tr>
<tr>
<td>Neuropsychological status</td>
<td>see Instruments</td>
<td>59</td>
<td>3rd M</td>
<td>1 × / y</td>
</tr>
<tr>
<td>Total body composition (only for obese patients with BMI&gt;3SD)</td>
<td>DEXA</td>
<td>63</td>
<td>every 2 years</td>
<td></td>
</tr>
</tbody>
</table>

5.2. Laboratory diagnostics

These encompass perioperative, intense monitoring of electrolytes and osmolality in order to diagnose acute osmolality pathologies (central diabetes insipidus). Early detection of polyuria/polydypsia DI phases, fluid regulation titration using i.v. drip infusion, NaCl substitution, and DDAVP drip infusion (see section on postoperative pharmaceutical treatments, p. 73).

5.3. Neuroradiology postoperative course monitoring

**Immediate postoperative course**

- If patient is in clinical stable condition: **MRI before and after gadolinium** enhancement. Early postoperative MRI examinations (within the first postoperative 48–72h) are not required because (in contrast to other malignant brain tumors) craniopharyngioma is not an intracerebral tumor.
- In cases of preoperative **CT tumor calcification** verification, it is recommended that native CT monitoring without gadolinium enhancement be performed during the first postoperative days, especially in cases of incomplete resection.
- **Submission of imaging results** (complete and incomplete resection): results are to be sent to study headquarter using assessment forms (pp. 155–159, 163).
- **Imaging film/CDs and findings are to be sent to** Prof. Warmuth-Metz, Würzburg, Germany.

**Longer term postoperative course**

- **No residual tumor after resection:** MRI before and after gadolinium enhancement every 3–6 months during 1st year and every 6–12 months afterwards up until 5 years following surgery.
- **Residual tumor / calcifications after resection:** MRI with contrast enhancement every three months during 1st year and annually for the first 5–8 years following surgery.
- **In clinical investigation** the indication for short-term, imaging course monitoring always arises
5. Postoperative diagnostics

- pre- and postoperative MRI for all patients
- preoperative CT without contrast enhancement for all patients
- postoperative native CT to monitor preoperative verified calcifications
- local image assessment of residual tumor progression for randomized treatment Arm I and Arm II patients
- monitoring examinations following irradiated randomized patients

5.4. Ophthalmological monitoring during follow-up
Every 3–6 month eye examinations including papilledema, visual acuity and field of vision are necessary during the first and second year after surgery and annually afterwards. Even more frequent eye examinations should be considered for irradiated patients (Form 5, p. 160).

5.5. Anthropometric monitoring during follow-up
Body height / length, weight, Tanner pubertal stage, and testicular volumes using Prader’s orchiometer should be measured every 6 months during the first year following surgery and annually afterwards. Left hand carpogram x-ray examinations using Greulich and Pyle standard atlas should be performed annually to determine bone age.

5.6. Functional capacity evaluation instruments

Function capacity assessment (Fertigkeitenskala Münster Heidelberg FMH, p. 129)
Wolff at al. developed and published a German questionnaire in 1978 (FMH) to measure QoL and functional capacity of patients with brain tumors. This scale includes 57 questions expressing the quality and independence level of daily life. The average time to answer the questionnaire is 4.5 minutes (Dabrock 1995). The FMH scale was normalized using 971 test subjects (45.5% female) between ages 0 and 101 and yielded age-specific percentile rankings. Its validity was verified by testing 10 pediatric brain tumor patients with different deficiencies. A positive correlation (r = 0.7) to the intelligence quotient exists (Däumling 1994), the FMH scale coinciding even better with semiquantitative assessments performed by treating physicians (p<0.001). Continuous measurements closely reflect QoL during the course of a disease (Dabrock, 1995). The FMH scale is a diagnostic component of the SIOP-LGG and HIT-HGG of the GPOH studies. Prospective, multicenter evaluations using the FMH scale make comparisons possible between craniopharyngioma patients and patients with low-grade gliomas of comparable anatomical localization (duration: 5 min.).

5.7. Neuropsychological evaluation instruments – course monitoring
These tests define a basic diagnostic and are recommended for estimating mental, sensory-motor, and fine motor functions three months following surgery and during annual postoperative examinations. Selection of measurements takes into consideration important key factors of strataums II and III in the well established CHC (Cattell-Horn-Carroll) cognitive abilities model. General use of the most current version of these measurements is recommended.

1. Bayley Scales of Infant and Toddler Development III – Screening Test (BSID III – Screening Test)
Author: N. Bayley 2005; for ages <3 y; duration 15–25 min.
BSID is an internationally established process for diagnosing infant and child development up to 42 months of age. The battery of tests makes it possible to test developmental status of representative cognitive, verbal, and motor skills and establish an initial idea of general intelligence (the so-called g factor). Implementation of BSID (2nd edition) was introduced in 2005 according to a decision of the German joint federal committee as a standard instrument for early age follow-up care.
The modified structure of BSID’s 3rd edition offers an enhanced interpretation of individual developmental categories. This new BSID edition recommends a specific procedure for patients less than 3 years of age. To maintain investigation emphasis on the low number of very young craniopharyngioma patients, screening of key development aspects in BSID III are to be sufficiently considered. Test results can be interpreted in terms of the CHC g (general intelligence) factor.

2. Coloured Progressive Matrices (CPM)
Authors: J.C. Raven, S. Bulheller & H. Häcker (3rd ed., 2002); for age groups: ≥4 to ≤11 y, duration: 5–10 min.

Raven's German Matrices Test offers a process for detecting inductive thinking capacity. Because inductive thinking represents a central aspect of fluid intelligence, the SPM and CPM (an abridged version of SPM) consider fluid intelligence factors to be good assessors of inductive thinking capacity. Both of these matrices tests also assess general intelligence (Spearman's g factor) and spatial thinking capacities. Thanks to Heller's, Kratzmeier's, & Lengfelder's (1998) more recent investigations, current German standards are now available for the SPM, making it possible to reveal a patient's inductive thinking capacity age.

CPM's avoidance of reasoning effectiveness is what sets it apart from SPM and SPM's young age limitations. In cases of poorly performing test persons when age limit is a problem, CPM can be used instead of SPM, rendering more interpretable results. Test results can be interpreted in terms of the CHC gf (fluid intelligence) factor.

3. Vocabulary-extent subtest
Hannover-Wechsler intelligence test for pre-schoolers III (HAWIVA-III) Authors: A. Fritz-Stratmann, G. Ricken, K.-D. Schuck & U. Preuß (2007); Hamburg-Wechsler Intelligence Test for Children IV (HAWIK IV) Authors: Petermann et al. (2007); Wechsler Intelligence Test for Adults (WIE) Authors: M. von Aster, A. Neubauer & R. Horn (2006); total age range: 3−<70 y; duration: 5−10 min.

Vocabulary extent is a measurement of crystallized intelligence or what is known as fact-based intelligence. Wechsler's age-relevant series of vocabulary subtests offer age-adapted tests for the relevant age spectrum. Because the vocabulary tests are conducted as a power test, a dependable estimate of retarded patients' achievement potential is also possible. The following correlation of patient age/test type is recommended: ≥3.0 y: HAWIVA-III; >6.6 y: HAWIK IV; >16 y: WIE. Test results can be interpreted in terms of the CHC Gc (crystallized intelligence) factor.

4. Number recall subtest: Kaufman Assessment Battery for Children (K-ABC)

Test estimates short-term/working memory capacity by scoring verbal recall of verbally-presented series of numbers. The K-ABC number recall subtest is appropriate for patients <12 y. The K-ABC II contains some additional (more difficult) items based on the K-ABC items and is appropriate for patients up to 18 y. Based on the assignment of tasks in the assignment material, use of the US American standards appears reasonable (applies to the >12 y standards of K-ABC II). Test results can be interpreted in terms of the CHC Gsm (short-term memory) factor.

5. The Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI) Author: K.E. Beery (1997); age group: 3−18 y; duration: ≤10 min.

The VMI assesses visual-motor integration abilities. The patient is presented with 24 increasingly complex geometric figures and asked to draw (copy) them. The test is user friendly and non-stressful for all age groups. Sufficient comparability testing of European achievement ratios with existing VMI US American standards has been carried out. Test results can be interpreted in terms of the CHC Gv (visual-spacial abilities) factor.
6. **Continuous Performance Test (CPT)**

Authors: M. Knye, N. Roth, W. Westhus, & A. Heine (2003); age group: 4–20 y; duration: 15 min.

CPT is a computer-aided procedure that is primarily intended to detect selective attention. The letters H, O, T, X, Z are presented on a screen. The task is to react with a pre-determined keystroke when an "O" follows an "X". In the currently available version (Hogrefe obtainable from test headquarters) there are two test phases interrupted by a 2-minute break. Attention diagnostics are based on differentiations of correct and incorrect keystroke responses. Omissions can be distinguished from mistakes.

The goal is to introduce an abbreviated CPT procedure that does not including the attention duration component to the HIT network (medium-term) therapy optimization studies.

Test results can be interpreted in terms of the CHC Gsm (short-term memory) factor.

7. **Instruments to detect observable behavioural features**

**Child Behaviour Checklist** (CBCL/4–18) parent questionnaire regarding their child’s/adolescent’s behaviour. Author: T.M. Achenbach; age group: 4.0–18.0 y.

This parent questionnaire (CBCL/4–18) regarding their child’s/adolescent’s behaviour is the German version of Achenbach’s *Child Behaviour Checklist*. The questionnaire surveys parental appraisals of their 4–18 y child’s competences, observable behavioural features, and observable emotional features. The child’s/adolescent’s competences are surveyed in the first part of the questionnaire and the second part of the questionnaire is devoted to 120 Items describing the child’s/adolescent’s observable behaviour and emotional traits plus any physical difficulties. Question-answering completion time: 20–30 min.; duration: 30 min.

8. **Neuropsychological testing**

Neuropsychological tests, especially since they document the disease course, should only be carried out at dependable, strictly-regulated centers that have the personnel resources for the planned duration of the study.

The testing is to be carried out in pediatric oncological centers that exhibit the neuropsychological diagnostic expertise set by the national G-BA resolution and test result data are to be made available to study headquarters. Diagnostically active colleagues at the pediatric oncological centers are required to participate in a workshop as a quality assurance measure to clarify test executions and secure uniformity. Patients who are treated at out-patient clinics that do not fulfil the above-mentioned criteria should be neuropsychologically tested at protocol-appropriate centers qualified as specified above. Travel costs for these patients will be reimbursed.
5.8 Detailed descriptions of health-related QoL test instruments (HIT-Leben)

Evaluation form for surveying craniopharyngioma patient life situation (HIT-Leben)
The HIT-Leben life situation questionnaire is based on life situations, social reintegration, and scholastic plus professional education experiences drawn from a retrospective survey of young adults following cancer treatment. Experience drawn from using the modified questionnaire in a different survey made it possible to improve the instrument even further. The questionnaire surveys parents and requires 10 minutes to complete.

PEDQOL (Pediatric QoL Questionnaire); German version by G. Calaminus 2000
PEDQOL is a cancer-specific instrument comprised of 50 Items. After defining health-related QoL, the questionnaire is composed of the following domains: physical functions, emotional well-being, social interactions, and cognition. In context of the disease, these theoretically-based domains are supplemented by especially relevant empirically-based "anatomy" and "physical condition" domains. PEDQOL surveys patient-perceived QoL, providing a patient-reported instrument of children and adolescents from 8 to 18 years of age. The children are asked to think about how they felt last week – this time period having been established in evaluation research as the optimal reference point for self-reporting experiences and/or functional conditions. Many children between 4 and 7 years can give a self-estimation of their well-being when the questionnaire is read to them by their parents. The parents should decide whether or not the child is able to comprehend the substance of the questions. The items in this parent-administered version for very young children are age-adapted, corresponding extensively with the PEDQOL 8–18 y version. PEDQOL uses a four-level Likert scale offering a choice of four possible answers per item. It was developed according to psychometric criteria and validated on both healthy and cancerous children.


CHQ is a generic instrument for assessing child and adolescent QoL. It is designed as a parent-answered version of the patient survey instrument for 5–15 year olds. The questionnaire is a general health assessment based on a scale ranging from excellent to poor regarding the child’s physical capacities, school work, pain, complaints, social interaction, general well-being, satisfaction with different areas of life, and their general state of health.

SDQ: Strength and Difficulties Questionnaire
SDQ is a short instrument that evaluates behaviour and observable features of behaviour. Self-reporting age span is from 11 to 16 and parent-reporting is used for patients from 4 to 16 years of age. The instrument can be applied in a diverse manner and is a component of QoL evaluations in international pediatric brain tumor studies (HIT/PNET IV).

EORTC QLQ-30 (European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire) and Brain Cancer Module QLQ-BN20
Cancer-specific EORTC QLQ-30 surveys statements regarding emotional, physical and social well-being as well as cognitive functioning, functional ability, and roll functioning for patients over 18 years of age. Disease-specific information regarding treatment-associated symptoms and problems is covered in the supplementary module QLQ-BN20.

The individual questionnaires are summarized in booklets to simplify data collection. The various booklets for patient and parent versions specifying the different evaluation age spans are outlined in the table on the next page.
Summary of schedule and instruments for surveying QoL (HIT-Leben)

Examination time points: 3\textsuperscript{rd} month (60–90 d) postoperative (pre XRT) and annually post OP relative to randomization (years 1–5)

<table>
<thead>
<tr>
<th>Age group</th>
<th>Parent survey booklets</th>
<th>Patient survey booklets</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥4 y – ≤7 y</td>
<td>Life-situation SDQ E  CHQ  PEDQOL 4–7 y FMH</td>
<td>≥4 y – ≤5 y PEDQOL preschool children</td>
</tr>
<tr>
<td>≥6 y – ≤7 y</td>
<td>PEDQOL (6) 8–18 y</td>
<td></td>
</tr>
<tr>
<td>≥7 y – ≤18 y</td>
<td>Life-situation SDQ E  CHQ  PEDQOL ≤18 y FMH</td>
<td>≥8 y – ≤10 y PEDQOL 8–18 y</td>
</tr>
<tr>
<td>≥11 y – ≤16 y</td>
<td>PEDQOL 8–18 y SDQ K</td>
<td></td>
</tr>
<tr>
<td>≥17 y – ≤18 y</td>
<td>PEDQOL 8–18 y FMH</td>
<td></td>
</tr>
<tr>
<td>&gt;19 y</td>
<td>EORTC QLQ-30+ QLQ-BN 20 FMH</td>
<td></td>
</tr>
</tbody>
</table>

These instruments for assessing QoL adhere to theoretical testing quality standards. They cover the predictable ages of children and adolescents with craniopharyngioma and the general aspects of their illness-specific quality of life. Their sensitivity to childhood development-contingent variations has been quantitatively verified. The instruments have been tested in populations of healthy children, providing the necessary foundation to compare the project’s patient deviations with tested norms. Patient perspectives vs. parent perspectives will also be reported.

The survey instruments appear well suited for applying scale selection to arrive at an optimized inter-scale compilation of these basic instruments. This enables consistent, timely and load-low detection of specific information regarding QoL for children and adolescents with craniopharyngioma. The compression of the basic instruments can then be applied to ancillary assessments that are important for measuring results of long-term consequences such as follow-up care.

QoL investigation plan
Using instruments to evaluate life situation and QoL is dependent upon patients agreeing to the following survey schedule. The following schedule is based on the different inquiry instruments specifically designed for age groups of 4–7, 8–18, or <19 years of age (see table).

<table>
<thead>
<tr>
<th>Evaluation of life situation and QoL (patients: 4–&lt;7 y)</th>
<th>Survey time points post OP (pOP) relative to post randomization (pR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survey</td>
<td>3\textsuperscript{rd} mth (60–90 d) post OP</td>
</tr>
<tr>
<td>LIFE SITUATION parent-reported</td>
<td>x</td>
</tr>
<tr>
<td>CHQ – parent-reported</td>
<td>x</td>
</tr>
<tr>
<td>SDQ – 4–16 y parent-reported</td>
<td>x</td>
</tr>
<tr>
<td>PEDQOL – patient-reported ≤18 y</td>
<td>x</td>
</tr>
<tr>
<td>PEDQOL – parent-reported</td>
<td>x</td>
</tr>
<tr>
<td>FMH – parent-reported</td>
<td>x</td>
</tr>
</tbody>
</table>
Practical approach

KRANIOPHARYNGEOM 2007 reports every new craniopharyngioma patient to the HIT-Leben project group using the German Pediatric Cancer Registry reporting fax established for HIT/PNET IV. For the 3rd month (60–90 d) post OP examination, the HIT-Leben project group will provide patients and their parents via the treating center with the following:

- letter from the project group (and when appropriate from study-leader) requesting participation in the survey
- written information regarding the survey
- participation consent form for the duration of the study
- self-addressed and stamped HIT-Leben project group return envelope
- booklet with appropriate survey instruments – 3rd month post (60–90 d)

Booklets necessary for the annual QoL inquiries will either be sent directly to the patient by the HIT-Leben project group or delivered via the participating center. It is the responsibility of the HIT-Leben project group to distribute the surveys and analyze the statistical data.

5.9. Measuring body composition (DEXA)

Body scans using the Dual-Energy X-ray Absorptiometry (DEXA) objectively measure the body’s adipose tissue and render a valid obesity gradation (Van Loan 1992). DEXA data are an elementary component of investigating incidences of obesity, risk factors and therapy (rehabilitation) for patients with craniopharyngioma. Regular body composition investigations using DEXA are recommended every 2 years to monitor the development of obesity (BMI>3SD). Comparable to bone age determination using carpogram, the DEXA nuclear medicine examination is a “recommended indication” of diagnostics during follow-up. The total radiation load amounts to appr. 0.01 mSv, ca. 1/100 of the annual exposure to natural sunlight, and is by a factor of 100 lower than the radiation load of a CT examination using a modern CT machine.

Body composition examination (DEXA) every 2 years for obese patients (BMI>3SD) only
5.10. Endocrine course diagnostics

Schedule

<table>
<thead>
<tr>
<th></th>
<th>6 months post OP</th>
<th>1x/year</th>
<th>every 2 years</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>anthropometric carpogram</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>height, weight, pubertal stage bone age (Greulich &amp; Pyle)</td>
</tr>
<tr>
<td>fT4, TSH</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>Frequency of endocrine course diagnostics in 1st year post-OP should increase if weight increase requires further evaluation.</td>
</tr>
<tr>
<td>IGFBP-3 or IGF-I</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td></td>
</tr>
<tr>
<td>daily cortisol profile of saliva or serum</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td></td>
</tr>
<tr>
<td>or: free cortisol in 24h urine collection</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td></td>
</tr>
<tr>
<td>DHEAS</td>
<td>○</td>
<td>○</td>
<td>○</td>
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<tr>
<td>LH/FSH (only [post]-pubertal patients) prolactin</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td></td>
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<tr>
<td>For obese patients</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>Examinations only for obese (BMI &gt; +3SD)</td>
</tr>
<tr>
<td>oGTT</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td></td>
</tr>
<tr>
<td>HbA1c</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td></td>
</tr>
<tr>
<td>Body composition exam. (DEXA)</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td></td>
</tr>
<tr>
<td>Endocrine testing</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>Endocrine hospital testing performed ca. 6th m post-OP. Discontinue medication according to test protocols (pp. 65, 119).</td>
</tr>
<tr>
<td>CRH-/TRH- test</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td></td>
</tr>
<tr>
<td>GnRH test (patients &gt;14 y)</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>GnRH test for patients &gt; 14 y</td>
</tr>
<tr>
<td>clonidine/arginine test</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td></td>
</tr>
</tbody>
</table>

3rd month (60–90 d) post OP: QoL (PEDQOL) baseline evaluation, randomization (fax: +49 (0)441-403-2789). Endocrine diagnostic testing, imaging.

6th month post OP: Approximately six months after surgery, endocrine diagnostics (age appropriate) are recommended together with an examination of the MRI imaging in order to either prove or rule out endocrine deficits. Growth hormone stimulation tests, releasing hormone tests (TRH-, CRF-tests and GnRH tests for patients > 14 y) should be carried out as well as a daily cortisol profile in serum and/or saliva or determination of free cortisol in 24h-urine collection after having previously discontinued medication (see next section). For patients irradiated 4 months postoperatively, tapering off or discontinuing medication should be rescheduled for sometime later.
Tapering off / discontinuing medication before endocrine diagnostics (6 months post-OP)

**Hydrocortisone:** An abrupt drop in hydrocortisone medication following a 4-6 month substitution to compensate for suppressed adrenocortical function, even if in recovery, would lead to a primary hypocortisolism, posing a threat to the patient and therefore is inadvisable. Dosage should be tapered off starting the 4th postoperative month for non-irradiated patients and under regular, weekly clinical monitoring. Patients whose pituitary was clearly identified and had to be resected during surgery are to be spared these tapering-off attempts and the releasing-hormone tests. In unclear surgical situations regarding the pituitary’s conservation and/or preservation, it is recommended to halve the daily hydrocortisone substitution dosage every week but maintain the dose distribution (morning dosage ca. 50% of daily dosage). In cases of intercurrent infections or other physical stress situations, tapering off hydrocortisone medication and/or the hospital diagnostic procedure should be postponed.

**Thyroxin:** In unclear surgical situations regarding the pituitary’s integrity and/or preservation, it is recommended to discontinue L-thyroxine medication four weeks before hospital endocrine diagnostics (basal and TRH-simulated thyroid gland parameters) in the 6th month following surgery.

**In the first postoperative year**
- anthropometric data (every 6 months)
- bone age according to Greulich & Pyle: carpogram (annually)
- Considering that **weight gain occurs early in first postoperative year in 50% of cases** and develops into severe obesity, monitoring the following parameters during the first 6 months following surgery is recommended:
  - IGF-BP-3 or IGF-I
  - thyroid parameters (FT4, TSH)
  - cortisol profile in serum or saliva, or free cortisol in 24h urine collection

**For irradiated randomized patients, discontinuation of endocrine medication and regular (appr. 3 month) testing should be postponed following irradiation.**

**Starting with the second postoperative year: annual monitoring**
- anthropometric data
- IGF-BP-3 or IGF-I, thyroid parameters (FT4, TSH)
- Cortisol profile in serum or saliva, or free cortisol in 24h urine collection.
  
  Interruption of hormonal substitution (L-thyroxine, hydrocortisone) is not done for purposes of monitoring thyroid values and the corresponding cortisol in serum/saliva/urine. The goal of the diagnostics is not to verify a secondary/tertiary hypocortisolism/hypothyroid but to assess hormone substitution and therapy optimization if necessary. Radioimmunological measured salivary cortisol concentrations correlate well with patient serum concentrations (Aardal 1995).
  
  - prolactin in serum
  - dehydroepiandrosterone-sulfate (DHEAS) in serum
  - for obese (BMI>3SD) patients only: HbA1c, (1x per year)
  
    oral glucose tolerance test (1x per year) p. 124
  
    body composition exam. (DEXA every 2 y) p. 63

  - clinical manifestations suggesting endocrine deficiencies (polyuria/polydypsia, adynamia, extreme weight gain, pathological growth rate) indicate that further diagnostics are necessary
  - not yet diagnosed DI, polyuria, polydypsia, nocturia: import/export capacities, especially values in morning urine, serum electrolytes and osmolality, DDAVP-test, p. 122
  - late pubertal development (Tanner PHI, BI, GI in girls ≥ 13y; boys ≥ 14y; premature puberty development (pubic arch: girls < 8y; boys: < 9y) or hypogonadism: sex-respective GnRH tests and estrogen or testosterone concentrations in serum
  - pathological serum concentrations of IGFBP-3 and/or IGF I, pathological growth rate or distinct weight increase: growth hormone stimulation testing (clonidine stimulation test, arginine stimulation test – if not yet carried out)
  - pathological low thyroid parameters (FT4, TSH): L-thyroxine substitution

**A higher frequency of monitoring endocrine parameters in the first postoperative year (every 3–6 months) is recommended in cases of early onset weight gain to preclude hormonal causes of obesity in craniopharyngioma patients!**
6. Pathology

Due to the difficulties encountered in making an exact brain tumor diagnosis in children, the study administration considers it vital that tumor specimens be submitted for all reported craniopharyngioma patients in order to make a uniform assessment. Specimen paraffin blocks and/or extractions of cystic fluid for every patient should be sent to the brain tumor reference center of the German Society for Neuropathology and Neuroanatomy (DGNN) in Bonn. All blocks will be returned promptly after processing. The material will be examined using conventional light-microscopic colour development and immunohistochemical reactions. Outside experts will be called upon for advice in unusual and/or diagnostically difficult cases. All findings will be compiled using the report form created for this therapy study and sent to both the local pathologist and the study secretary. Standardized histopathologic investigation parameters of each patient will be collected in a database program. Investigation material and the database will be at the disposal of all study colleagues for co-appraisal. This diagnosis strategy implements WHO tumor classification criteria, coinciding with the implementation of the newest version of WHO tumor classification (Kleihues 1996).

Reference pathologist: Prof. Dr. Torsten Pietsch
Institute of Neuropathology
University Hospital Bonn
Sigmund-Freud-Str. 25
53105 Bonn
Germany
Tel: +49 (0)228-2876602, Fax: +49 (0)228-2874331
E-mail: neuropath@uni-bonn.de

With consideration to collaborative studies and also the repository of processed tumor material, the study administration would like to appeal at all therapy centers to make their material available to the following investigations:

<table>
<thead>
<tr>
<th>Epigenetic regulation disturbances in origins of craniopharyngiomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prof. Dr. Michael Frühwald M.D., Ph.D.</td>
</tr>
<tr>
<td>University Hospital Münster, Germany, Pediatric Hematology and Oncology</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor suppressors and oncogenes in craniopharyngioma and angiography profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prof. Dr. Willem Kamps, Dr. E. de Bont</td>
</tr>
<tr>
<td>University Hospital, Groningen, the Netherlands</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Activation of Wnt signaling pathway in craniopharyngiomas and its clinical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prof. Dr. Torsten Pietsch</td>
</tr>
<tr>
<td>Institute of Neuropathology, University Bonn, Germany</td>
</tr>
</tbody>
</table>

**Biocase** dry ice transport boxes available at the pediatric oncological departments in Germany should be used to transport biological samples. For the above-mentioned investigations, a blood sample (5 ml heparin blood sample) should be included with the unattached tumor tissue specimen for reference DNA uses (pp. 108–109: Collaborative studies). Tumor tissue specimens along with associated serum, cerebrospinal fluid, and cystic fluid will be archived in a tissue-/material bank. On inquiry and with approval of the study commission, tumor material will be made available to other scientific investigations as well as participants in KRANIOPHARYNGEOM 2007.
7. Therapy

7.1. Neurosurgical therapy

An attempted complete microsurgical resection preserving adjacent regions is considered the therapy of choice for a childhood craniopharyngioma at primary diagnosis. The final decision regarding the degree of resection is made intraoperatively by the operating surgeon based on actual anatomical conditions. The intervention should be performed by a surgeon experienced in this area. A retrospective review of 139 children with craniopharyngioma who had undergone complete microneurosurgical resections revealed that the quality of life of patients depended significantly on the experience of the operating neurosurgeon. If a neurosurgeon resected two or more craniopharyngiomas per year, 87% of patients had a postoperative QoL classified as good. If a surgeon resected less than two craniopharyngiomas per year, only 52% of patients with a complete resection had a postoperative QoL classified as good (Sanford 1994).

KRANIOPHARYNGEOM 2007 ascertains and analyzes therapeutic strategy data and the postoperative outcome of patients. Recommendations regarding surgical procedure cannot be given due to the lack of valid data. It is the goal of the study, based on prospectively ascertained data regarding remission status and QoL, to generate hypotheses on the efficiency and compatibility of presently used surgical strategies that could be prospectively tested in a subsequent study.

7.2. Irradiation of craniopharyngiomas

The basic aim is a combined neurosurgical and irradiation procedure, based on a joint preoperative multidisciplinary consultation. The following strategies are proposed:

- follow-up monitoring after complete resection (R₀)
- for relapse cases: irradiation when appropriate after a repeat of neurosurgical intervention
- for inoperative R₁ or R₂ resections (incomplete):
  a.) for patients < 5 years of age (option-based decision)
     - local irradiation target volume of 54 Gy dose level (ICRU₅₀) (single dose 1.8 Gy) or
     - wait-and-see approach with MRI monitoring of progression: in case of progression irradiation as specified above
  b.) for patients ≥ 5 years of age (randomization)
     Arm I: immediate postoperative local irradiation with target volume of 54 Gy dose level (ICRU₅₀) (single dose 1.8 Gy)
     Arm II: wait-and-see approach using MRI monitoring of progression (>25%): irradiation in case of progression as specified in Arm I
- Postoperative assessments following incomplete resections in children under 5 should be performed to track any sign of tumor progression.
7.2.1 Irradiation treatment plan for relapses

Radiation therapy plays a major therapeutic role in case of tumor relapses. The extent of an attempted surgical resection of a relapsed tumor is based on localization and age of patient, requiring the multidisciplinary treatment team in order to make a responsible decision. Irradiation should only be performed on an exception basis for infants and children under 5 due to the age-related vulnerability of adjacent brain tissue.

Timing / therapy duration of irradiation for relapses
Irradiation should be administered between 3 and 12 weeks following surgery or as soon as possible after relapse diagnosis if no repeat surgery is performed.

Pauses during irradiation
The total permissible treatment pause is 2 weeks (4 treatment days per week). Study headquarters must be informed in order to discuss treatment options if therapy pauses need further extension.

Total dosage / fractionation
All patients are to receive treatment 1 x per day, 5 x per week. All planned fields should receive a fractionation of 1.8 Gy per session. The total dosage should be 54 Gy.

Irradiation plan of tumor region

<table>
<thead>
<tr>
<th>CNS segment</th>
<th>Number of fractionations</th>
<th>Dosage per fractionation (1x d)</th>
<th>Total dosage</th>
<th>Total duration (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor region</td>
<td>30</td>
<td>1.8 Gy</td>
<td>54.0 Gy</td>
<td>6.0</td>
</tr>
</tbody>
</table>

Planning target volume / irradiation technology
CT-supported therapy planning should be conducted using today’s available technology. CT planning enables the evaluation of integral dosage within the target volume as well as assessment of the organs at risk.

Irradiation of the primary tumor region
Clinical target volume is determined by postoperative CT or MRI depicting the tumor region (CT contrast-agent reinforced and/or T₁-weighted, contrast-agent reinforced MRI) that includes the preoperative area adjacent to the tumor along with a 0.5 cm safety margin. Depending on the geometric precision of the applied technology, the planning target volume is ascertained by the clinical target volume – as a rule within 0.3 to 0.5 mm. Consultation with the reference center / study administration is requested in cases of tumors with very large dimensions. The following risk organs are to be outline when preparing the dose-volume histograms (DVH): brain stem, optic chiasm, pituitary gland, optical nerve, bulbar, optic lenses, thalamus, hypothalamus, and both inner ears. An image fusion using diagnostic MRI must be created to define planned target volumes and risk organs. The interval between the therapy planning MRI and the CT-supported therapy planning must be no more than 21 days. As a rule, a three-dimensional conformal radiation therapy (3DCRT) plan with predictive assays is applied. A spherical configuration of the clinical target volume means that convergence radiation technology can also be used. In this situation, dose specification orients itself towards stereotactic one-time radiation therapy.
Dose specifications (ICRU-50/62)
Dose specifications are oriented towards the ICRU 50/62 report. If possible, the target volume should be irradiated within a tolerance range of 95% to 107%. Dose maximum and minimum within target volume as well as possible dose "hot spot" peaks (maximums outside of target volume range) are documented.

Patient fixation system / quality control
The fixation system should render a geometric precision of 1.0 to 1.5 mm with maximal deviations of 3.0 mm (Becker, Kortmann 1999) in order to realize the designated margins. Quality control measures are carried out according to participating centers’ proven procedures. Orthogonal verification of stereotactic target coordinates can be reproduced by the radiology therapy machine and compared to the radiographic projections generated by irradiation planning documentation. Reproduction of isocentric reference frames before the first irradiation is pivotal. Geometric precisions should be reproducible via once-a-week monitoring.

Acute maximum side-effects of irradiation
Brain pressure symptoms such as headaches, nausea and vomiting can arise during irradiation treatment and are to be symptomatically treated (see "Ancillary therapies" below).

Monitoring examinations during irradiation
Patient monitoring during irradiation should include neurological monitoring examinations as well as monitoring of osmolality and endocrine conditions when necessary.

Ancillary therapies
Oral administration of dexamethasone (e.g. 3 x 1 mg/m²/d) can relieve or completely eliminate brain pressure symptoms such as headaches, nausea and vomiting. Several weeks or even months after completion of irradiation treatment, children can develop radiation somnolence syndrome, which mostly even after a coexisting pathological EEG (electroencephalogram) conditions completely disappears. Alopecia in the radiation field is associated with cranial irradiation and is usually totally reversible.

Deviations from irradiation protocol
Minor deviations from irradiation treatment protocol are defined as:
- an interruption in treatment for technical reasons of no longer than 3 days between each session
- deviations of irradiation dose +/- 5%
- interruption of irradiation for less than a week

Major deviations from irradiation treatment protocol are defined as:
- deviations from dose and/or treatment time greater than above-defined minor deviations
- more than three weeks deviation from total planned treatment period
- deviations from target-volume dosage concept (p. 20)

Along with the completed radiation therapy forms, we ask that the irradiation plans, field simulations with field control logs, single-dose, and initial disposition of therapies also should be submitted.

Further irradiation options
It is the opinion of the radiooncolical reference center of the study that for reasons related to radiation biology, stereotactic single-dose convergence irradiation (linear radiation/gamma knife) has no relevance for the treatment of craniopharyngiomas. It is not yet clear how useful this technology is as the primary treatment or an option in relapsed cases. For this reason, no target volume or dose guideline can be given. The irradiation strategy should be left up to the treating radiooncologist.
Stereotactic instillation of radioisotopes such as $^{90}$Yttrium has been discussed as an alternative, experimental therapy for predominantly monocystic craniopharyngioma relapses (Lunsford 1994). Its radiogenic fibrosis and functional destruction of the fluid-producing cystic epithelial structures is postulated as a pathophysiological strategy. Degeneration of the cyst can be achieved 80–88% of the time with a 5 y overall survival rate of 80% (Voges 1997). However, this treatment approach to cystic craniopharyngiomas is limited and should only be used for postoperative relapse cases and only after percutaneous radiology treatment has been considered. Neuroradiological clarification should be obtained as to whether cystic leakage is present before considering stereotactic instillation of radioisotopes. If such a leakage is verified, the instillation is contraindicated based on side-effects due to dangerous side effects of leaking radioisotopes (see p. 34 for background).

7.3. Irradiation procedure – residual tumor progression following incomplete resection (Treatment Arm II of randomization study – postoperative wait-and-see strategy)

Randomization based on timing of postoperative irradiation after incomplete resection is planned for patients $\geq$ 5 years of age. Neurosurgical therapy options should be considered (cystic catheter for cystic progressions) for progressions of residual tumor after irradiation for patients in Treatment Arm I (immediate irradiation post-OP). Protocol-compliant irradiation will be performed following subsequent neurosurgical intervention for progressions of residual tumor for patients in Treatment Arm II (progression-contingent irradiation). Execution of irradiation is procedurally identical to immediate postoperative irradiation.

Draining predominantly cystic relapses with a catheter does not influence growth of solid tumor structures but can be complicated by a catheter occlusion. Appearance of additional cysts requires subsequent surgical intervention. Implanting a Rickham reservoir offers the possibility of necessity of repeated cyst reliefs but frequently achieves only temporarily pressure relief. Complete resection of a craniopharyngioma relapse is made more difficult by local postoperative alterations: These alterations frequently cause problems to discriminate between the relapse or residual tumor remnants and vascular structures, nerves and brain tissue – especially in the hypothalamic area.

Instillation of sclerosing substances into tumor cysts (bleomycin)

Instillation of a sclerosing agent (bleomycin) into craniopharyngioma cysts stereotactically or via an open implanted catheter is useful in cases of subsequent resection of cyst relapses and other difficult anatomical situations (Cavalheiro 1996). Radiological exclusion of leakage by instillation of a contrast agent is required before intracavitary treatment. It is also imperative that the cyst membrane be sufficiently thick. Cavalheiro et al. performed a 10 mg bleomycin instillation daily over 8 days before cystic fluid was aspirated. Takahashi et al. treated 7 craniopharyngioma patients (ages 2–13 y) two weeks after biopsy with an instillation of bleomycin (1–5 mg/every 2nd d; cumulative dosage: 13–95 mg) via implantation of an Omaya reservoir. Instillation of sclerosing substances into cysts does not impede growth of solid tumor structures (Takahashi 1985).

Consultation with study administration is requested concerning further, non-irradiation treatment strategies for tumor progression patients that are not randomized (those patients <5 years and all complete resection patients).
7.4. Definitions of resection grades and tumor response to irradiation

KRANIOPHARYNGEOM 2007 uses a modified version of the minimal criteria used by the Low Grade Glioma Study (SIOP LG G) to define resection grades and irradiation responses according to the recommendations of the SIOP Brain Tumor Subcommittee for low grade gliomas (Gnekow 1995).

**Intended degrees of surgical resection**
- total extirpation
- incomplete resection
- biopsy sample

**Classification of the degree of resection**
Classification of the degree of resection relies on the neuroradiologist and surgical data, giving priority to the neuroradiologist's classification with the surgical report considered as supporting data. Both solid and reproducible cystic parts of the tumor need to be taken into account. The analysis performed by the neuroradiology reference center takes both tumor forms into consideration.

<table>
<thead>
<tr>
<th>Degree of resection – based on surgical conclusions</th>
<th>Radiological</th>
<th>Surgical</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1 – complete resection, no microscopically discernable residual tumor remnant, cyst membrane completely resected</td>
<td>R1 complete</td>
<td>S1 complete</td>
</tr>
<tr>
<td>S2 – discernable residual tumor remnant</td>
<td>R2/R3 complete res. or rim/calcification</td>
<td>S2 residual tumor remnant</td>
</tr>
<tr>
<td>S3 – biopsy</td>
<td>R4 minimal change</td>
<td>S3 biopsy</td>
</tr>
<tr>
<td>S4 – cyst puncture, cyst drainage</td>
<td>R2/R4</td>
<td>S4 cyst puncture, drainage</td>
</tr>
</tbody>
</table>

Complete resection is diagnosed only when surgical and radiological assessments agree (S1–R1).

Incomplete resection
Small residual tumor remnant is left behind representing potential for local invasive growth that, under neuroradiology examination, can and sometimes cannot be identified as garland-shaped contrast agent enrichment or an isolated calcification (S2, R1–R2).

Incomplete resection
Postoperative neuroradiology examination reveals measurable tumor of a definable size that may or may not match surgical assessment (S1–3, R3).

Biopsy
Surgical and radiological results need to match in biopsies (S3, R4).
Surgical resection grades are defined as follows:

**Complete resection**
No discernable tumor at the surgical site upon conclusion of extirpation (as stated in surgical report). Possible cysts were completely resected along with cystic membrane – results confirmed by postoperative MRI examination using contrast agent. If preoperative CT revealed calcifications, native CT imaging without contrast enhancement needs to be done to verify classification as a complete or incomplete resection.

**Incomplete resection**
Every postoperative residual tumor remnant needs to be confirmed by postoperative CT or MRI before and after contrast enhancement. The extent of tumor resection must be measured in these cases by comparing pre- and postoperative CT / MRI imaging.

**Biopsy**
Biopsy surgery is undertaken exclusively to gain material for histopathological diagnostics.

**Cystic pressure relief**
Surgical intervention is undertaken only to achieve pressure relief via puncture, cystic wall fenestration, or catheter implantation. Diagnosis is made on the basis of cytological examination of extracted fluid.

**Criteria for tumor response to irradiation**

**Method for neuroradiological tumor volume calculation**
Three-dimensional tumor volume calculation – whether it be a primary tumor, residual tumor remnant, or relapse – is made possible using the rotation ellipsoid formula: \( a \times b \times c/2 \). Cystic portions are then subtracted from the total tumor volume, whose volume in turn is determined using the same formula.

**Complete response**
CT / MRI images give no radiological indication of residual tumor remnant.

**Partial response**
Tumor reduction is > 50% (see Tumor volume calculation, p. 137).

**Objective response**
Reduction radiologically measuring between 25 and 50% of all unambiguous residual tumor remnants. There are no indications of tumor progression or discernable new tumor lesions.

**Disease stabilization**
Tumor volume reduction is < 25% measured at convergence point of the two maximals: vertical tumor diameter perpendicular to horizontal diameter. There is no radiological indication of tumor progression.

**Tumor progression**
Each radiological proof of either tumor progression with a tumor volume increase > 25%, or a new lesion.

Development of an isolated hydrocephalus or other clinical indications of a possible tumor progression should not be automatically appraised as tumor growth. Care should be taken to ascertain whether a neurological deterioration exists such as an increased cortisol response to stress situations, other endocrine deficits, convulsions, or postconvulsive disturbances. This study regards a complete, impartial, objective response as well as disease stabilization as positive responses.
7.5. Pharmaceutical treatments

7.5.1. Central diabetes insipidus
Treatment of choice for central diabetes insipidus is desmopressin (DDAVP: 1-desamino-8-D-arginine vasopressin). DDAVP is an arginine vasopressin analogue that bonds only to antidiuretic V2 vasopressin receptors and therefore has no circulatory side-effects. Because of its missing alpha amino chain, DDAVP has a much longer half-life than AVP.

Available desmopressin (DDAVP) preparations in Germany

<table>
<thead>
<tr>
<th>Brand name (Germany)</th>
<th>Administration</th>
<th>Concentration</th>
<th>Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minirin® with Rhinyle®</td>
<td>nasal solution</td>
<td>250 µg / 2.5 ml</td>
<td>5 – 20 µg</td>
<td>8 – 20 h</td>
</tr>
<tr>
<td>Minirin Rhinette®</td>
<td>single dose pipettes for nasal application</td>
<td>20 µg / 0.2 ml</td>
<td>20 µg</td>
<td>8 – 20 h</td>
</tr>
<tr>
<td>Minirin® nasal spray</td>
<td>nasal spray</td>
<td>ca.10 µg / per metered dose</td>
<td>10 – 30 µg</td>
<td>8 – 20 h</td>
</tr>
<tr>
<td>DDVP 0.1 mg tab.®</td>
<td>tablets</td>
<td>100 µg tab.</td>
<td>0.1 – 0.8 mg</td>
<td>12 h</td>
</tr>
<tr>
<td>Minirin 0.2 mg tab.®</td>
<td>200 µg tab.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minirin parenteral®</td>
<td>subcutaneous, intramuscular, intravenous inj.</td>
<td>4 µg / ml</td>
<td>1 – 4 µg</td>
<td>12 – 24 h</td>
</tr>
</tbody>
</table>

The antidiuretic effect of a nasal administration of 20 ug DDAVP lasts approximately 10 h. The biological availability of nasal administration is 10% vs. 1% oral administration. Nasal administration of 20 ug DDAVP, 1 ug i.v. and 400–600 ug orally render approximate equivalent doses but important intra- and interindividual variations exist in these comparisons.

Perioperative treatment of central diabetes insipidus - Osmolality balance maintenance
DDAVP administration: Intraoperative and early postoperative ADH (DDAVP) osmolality and body fluid balance maintenance is accomplished by continuous infusion of DDAVP, i.v. saline solution drip, bladder catheterization, and close monitoring of body weight/urine osmolality/serum electrolyte ratios.

Treatment strategy (Lehrnbecher 1998)

- Exact, constant fluids input / urine output monitoring (bladder catheter)
- Polyuric conditions require i.v. fluid substitution due to over excretion of urine and perspiration
- During polyuric phases, fluid is replaced exclusively via i.v. infusion of saline-free solutions
- If DI symptoms (polyuria) persist for more than 2hrs or fluid loss substitution is no longer successful:
  1.) reduce DDAVP i.v. dose (4–20 ng/kg i.v. bolus)
  2.) withdraw fluid input
  3.) replace with i.v. fluid substitution solutions of a higher saline concentration (0.7–0.9% NaCl)
- If polyuria persists: replace DDAVP i. v. bolus with higher dose of DDAVP
- If polyuria reoccurs: repeat DDAVP i.v. bolus
- SIADH (syndrome due to inadequate ADH secretion) can develop in rare instances, characterized by oliguria without prior DDAVP supplementing, increase in osmolality/body weight ratio, and a decrease in serum sodium concentration.
If SIADH occurs:
1.) immediately withdraw fluid input
2.) replace with i.v. fluid substitution solutions of a higher saline concentration (0.7–0.9% NaCl)

When diabetes insipidus and other apparent resistances to DDAVP therapy occur, case-specific DDAVP dose requirements should be considered and increased accordingly. The following DDAVP enhancers are discussed in the literature (Reeves 1998):

### Adjuvant pharmaceuticals for diabetes Insipidus

<table>
<thead>
<tr>
<th>Pharmaceutical</th>
<th>Admin.</th>
<th>Dose</th>
<th>Duration</th>
<th>Important considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>thiazide diuretics</td>
<td>p.o.</td>
<td>50–100 mg/d</td>
<td>12 – 24 h</td>
<td>high serum Na(^+) concentrations reduce effectiveness</td>
</tr>
<tr>
<td>chlorpropramide</td>
<td>p.o.</td>
<td>250–750 mg/d</td>
<td>24 – 36 h</td>
<td>useful for partial DI cases</td>
</tr>
<tr>
<td>caveat: hypoglycemia!</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>clofibrate</td>
<td>p.o.</td>
<td>250–500 mg every 6–8 h</td>
<td>6 – 8 h</td>
<td>useful for partial DI cases. caveat: frequent side-effects!</td>
</tr>
</tbody>
</table>

### Cerebral salt wasting syndrome (CSW)

Hyponatremia accompanied by elevated urine sodium are characteristic conditions of cerebral salt wasting syndrome. Increased plasma concentrations of brain natriuretic factor (BNF) and lowered serum mineralocorticoid concentrations have been postulate as pathogenic factors of CSW (Berendes 1997). Cerebral salt wasting syndrome was described in patients with various CNS diseases of the sellar / parasellar masses (Nakayama 1999). In hyponatremia, CSW must be differentiated from SIADH as the two require different therapeutic strategies (Ganong 1993; Laredo 1996). Fluid restriction in cases of CSW is contraindicated. Sufficient fluid substitution via an i.v. infusion of high-saline (NaCl) solution is necessary. Favourable effects of mineralocorticoid administration have been described. Both hydrocortisone and fludrocortisone have been verified as being therapeutically effective (Berendes 1992; Sakarcan 1998).

### Long-term therapy for diabetes Insipidus

DDAVP nasal solution is recommended for use in children and infants. As small children and infants frequently require lower dosage (0.15–0.5 ug/kg/d), it is recommended to dilute the DDAVP nasal solution with physiological saline solution (1:10) (i.e. 1 ug DDAVP = 0.1 ml of the 1:10 of diluted Minirin Rhinyle\(^{®}\) solution, availible in Germany). A nasal spray is available (ca. 10ug/per metered spray) for patients requiring more than a 10 ug DDAVP single dose. DDAVP is administered preoperatively using an intravenous drip infusion and postoperatively in cases of impaired nasal reabsorption, especially after transsphenoidal surgical access resections (0.03–0.12 ug/kg body weight per dose). The first step in approaching long-term diabetes insipidus therapy is establishing an evening DDAVP dosage that enables the patient to sleep without nocturia (excessive nighttime urination). The dose should be selected so that diuresis is reinstated in the morning hours. It bears mentioning that DDAVP dose regulation is subject to quite a wide intra- and interindividual range.

DDAVP overdose or uncontrolled fluid absorption due to DDAVP, especially interferences in thirst regulation, can cause overhydration and hyponatremia. The morning DDAVP dose should be administered only after polyuria occurs, sparing the patient polyuria phases during the day. Ideal dosage adjustments can eventually make only morning and evening DDAVP administration necessary. In individual cases, more frequent administration may be necessary – especially around lunchtime. A varying DDAVP requirement is typical during the initial weeks following surgery. Lateron, infections of the upper air passages (rhinitis) can cause reduced or enhanced nasal absorption, requiring an adaptation of dosage.
Perioperative brain edema prophylaxis (OBLIGATORY):  Dexamethasone (ca.8 mg/ m² BSA/ 4 x d / every 6 hrs)

7.5.2. Hypocortisolism
Perioperative dexamethasone therapy for brain edema prophylaxis makes hydrocortisone substitution unnecessary. Early postoperatively (few days following surgery), dexamethasone should be tapered off and overlapped with conversion to hydrocortisone substitution (10–20 mg/qm/d, 2–3 doses, ca. 50% total day dose mornings, ca. 30% at noon, ca. 20% evenings). During short periods of physical stress situations (headaches, fever, infection, etc.) it is necessarily to temporarily triple the substitution dosage. Hydrocortisone substitution therapy needs to be noted on the patient’s emergency medical card.

7.5.3. Hypothyroidism
Levothyroxine substitution: (ca. 100ug/qm/d p.o.). Thyroid gland parameters (FT4, TSH) should be monitored 6–8 weeks after therapy begins, repeated every 6–12 months or whenever clinical symptoms appear (tiredness, exhaustion, etc.).

7.5.4. Growth hormone deficiency
Hypothalamic-pituitary growth hormone deficiency should be lab-test verified during follow-up examinations 6 months following surgery of craniopharyngioma or its diagnosis before embarking on growth hormone substitution. Postoperative GH stimulation tests do not appear to be particularly meaningfully in regard of surgical data on the resection of the pituitary gland. However, a consultation with responsible cost carriers and/or statement regarding reimbursing of costs is recommended before introducing growth hormone substitution (in Germany). Two growth hormone stimulation tests (clonidine test, arginine load; test protocols and procedures, pp. 121–123) verifying growth hormone deficiency are required. Pathological results in GH-stimulation testing and a growth rate <10th percentile according to Prader or extraordinary weight gain call for recombinant growth hormone substitution.

Growth hormone substitution
For prepubertal and pubertal patients, a single daily dose of 0.025–0.035 mg per kg body weight is administered via subcutaneous injection. Increasing dosage during puberty has been recommended, but controlled studies regarding favourable effect of such an increase do not exist.
For postpubertal patients, recombinant growth hormone substitution is indexed and reimbursed by health insurers (in Germany) according to laboratory verification (two pathology stimulation tests) of a hypothalamic-pituitary growth hormone deficiency. Under close monitoring of IGF-I serum concentrations, substitution begins with a low dose of 0.15 mg/d, gradually increased to a maximum daily maintenance dose rarely exceeding 1.0 mg subcutaneously injected. Possible side-effects: Side-effects, particularly in adulthood, are edema, pseudotumor cerebri, arthralgias, myalgias and psychological alterations – requiring a dose reduction or, when appropriate, termination of substitution therapy.

There is no proven correlation between growth hormone substitution and the risk of relapse or progression of childhood craniopharyngiomas.
7.5.5. Hypogonadotropic hypogonadism

Therapy in boys
Puberty induction options, timing, and body development effects should be discussed starting at a chronological patient’s age of 14 year (Holl 1993). Eventual height prognosis and emotional pressures suffered due to delayed puberty need to be taken into consideration. The decision regarding the three options for treating hypogonadotrophic hypogonadism should be based on the boy’s age and the therapy aim (puberty development, testicle growth or fertility):

- **Testosterone** substitution to induce puberty: Testosterone administration is the treatment of choice for inducing puberty in male pediatri c patients. Appropriate dosage is based on the physiological puberty stage:
  
  Testoviron Depot®: initially: once-a-month 50 mg i.m. (intramuscular) injections  
  after 12 months: once-a-month 100 mg i.m.  
  after 24 months: 250 mg i.m. every 3–4 weeks

  Patients are frequently disappointed with how "slow" puberty signs develop. It is best to point out the amount of time physiological puberty requires to develop and that testicle volume remains slight during testosterone substitution. Permanent testicular damage has not been reported.

- **HCG/HMG** treatment: if for psychological reasons the therapy aim is testicular growth, intramuscular injections of HCG (Predalon® – German version of Pregnyl®, Pregesin®, and Primogonyl® – German version of Profasi®) can be used. Initial recommended dosage is 2–3 injections per week of 500 to 1000 IU, later increasing to 2500–5000 IU. Dosage is based on clinical results and serum testosterone levels. If the therapy aim is fertility, an additional HMG i.m. (Pergonal®) is usually necessary (3 injections per week of ½–2 75 IU). It is also recommended if HCG-only therapy results in insufficient testicular growth. Gynecomastia (male breast enlargement) is a frequent side-effect of HCG therapy.

- **Pulsatile LHRH therapy** – only for hypothalamic disorders: This pump therapy procedure is very costly and inappropriate for pediatric patients as it is used in males for sperm-count failure due to HCG/HMG therapy.

Therapy in girls
Puberty induction options, timing, and body development effects should be discussed with 13–14 year old female patients and their parents (Holl 1993). As with boys, eventual height prognosis and emotional pressures suffered due to delayed puberty need to be taken into consideration.

**First 6–12 months:** 0.3 mg/d natural estrogen (1 tab.Presomen® 0.3) 3 wk followed by 1-wk break

**After 6–12 months:** 0.6–0.9 mg/d natural estrogen (1–1.5 tab. Presomen® 0.6) 3 wk +  
the synthetic oral progestin Norethisteron (Primolut Nor® 5) in the 4th wk  
or switch to a sequence drug (Trisequens®, Cycloprogynova®, or Presomen®  
0.6/1.25 tablet).

**Fertilization treatment:** pulsatile LHRH pump therapy (only as directed by a gynecologist)

**Planning and execution of endocrine diagnostics and therapy must be done by a pediatric endocrinologist!**
8. Long-term treatment evaluation

Evaluating the long-term consequences of these treatments is one of the most important goals of KRANIOPHARYNGEOM 2007. It is therefore imperative that at the beginning of treatment, an assessment be made of the numerous diagnostic results regarding the patient's anthropometric, endocrine, ophthalmologic, intellectual, and psychological status (see Preoperative diagnostics, Section 4, p. 52).

Long-term diagnostic and therapy standardization, evaluation and quality control were chief aims of KRANIOPHARYNGEOM 2000 and are also goals of its follow-up study, KRANIOPHARYNGEOM 2007. The following goals been set in order to develop a long-term care program (see Section 8.1, p. 78):

- standardization of endocrine diagnostics and substitution therapy
- quality control of endocrine, imaging, ophthalmologic and neuropsychological follow-up diagnostics
- quality control of hormone substitution therapy

The extent of data acquisition regarding postoperative endocrine substitution therapy is limited in KRANIOPHARYNGEOM 2007. Hormone substitution dosage data is not included in the scope of KRANIOPHARYNGEOM 2007. Data acquisition is restricted to which hormone axis requires substitution.

Every participating center, in collaboration with a pediatric endocrinologist, should make every effort to provide continuing follow-up care for patients whose age is far beyond the pediatric age group.

Radiooncological follow-up in accordance with radiation protection legislation

All patient examinations must be systematically monitored once a year by a radiooncologist. The corresponding documentation forms should be filled out and sent to the radiation reference center, Department of Radiation Therapy, University Leipzig:


Treatment-associated long-term effects of radiation therapy for malignant diseases in children and adolescents

Study director: Prof. Dr. N. Willich, Clinic and Policlinic for Radiooncology, Albert-Schweitzer-Str. 33, 48149 Münster, Germany; Tel: +49 (0)251-8347384, Fax: +49 (0)251-8347355; E-mail: radtox@uni-muenster.de.

Background

Radiation therapy is essential for treating tumors in children and adolescents, especially craniopharyngiomas. As in every therapeutic procedure, there is a cost/benefit ratio between expected benefits and side-effects. It is crucial that local monitoring detection rates closely correspond to induced side-effects detection – especially long-term effects. The German Working Group Pediatric Radiation Oncology (APRO or Arbeitsgemeinschaft Pädiatrische Radioonkologie) has designed a comprehensive study approach for detecting radiation side-effects in children and adolescents. The key detections are documented in the RiSK "Registry for the evaluation of late side effects after radiation in childhood and adolescence". See English version website for details: http://www.rojournal.com/content/3/1/10.

Approach for detecting radiation therapy long-term consequences

Radiation therapy techniques and irradiation dose exposure to risk organs are documented by the radiooncologist on a per-case basis and sent to the central registrar. Two months after therapy has ended, radiation therapy and its consequences are examined annually to detect side-effects and classified using the RTOG/EORTC score. Tumor related follow-up care remains the exclusive domain of the responsible pediatrician.
### 8.1. Long-term consequences, follow-up programs and documentation of the follow-up care in KRANIOPHARYNGEOM 2007 (> 1 year postoperative)

<table>
<thead>
<tr>
<th>Examination</th>
<th>Program</th>
<th>Timing</th>
<th>Documentation/evaluation form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthropic</td>
<td>height, weight, head circumference</td>
<td>annually</td>
<td>Form 5, p. 160</td>
</tr>
<tr>
<td>History</td>
<td>see assessment forms</td>
<td>annually</td>
<td>Forms 5 &amp; 6, pp. 160, 161</td>
</tr>
<tr>
<td>Bone age</td>
<td>X-ray left hand</td>
<td>annually</td>
<td></td>
</tr>
<tr>
<td>Body composition</td>
<td>DEXA (only for obese patients, BMI &gt; 3SD)</td>
<td>every 2 years</td>
<td></td>
</tr>
<tr>
<td>Endocrine (basal values)</td>
<td>IGF-I or IGFBP-3, fT4, TSH, prolactin, testosterone/estrogen as appr., cortisol level: 24h urine collection or daily profile in saliva or serum, HbA1c (for obese patients BMI&gt;3SD)</td>
<td>annually</td>
<td>Form 5, p. 160</td>
</tr>
<tr>
<td>Endocrine (testing)</td>
<td>clonidine test, arginine load test, TRH test, GnRH test, CRH test, oGTT (for obese patients BMI&gt;3SD)</td>
<td>only as required (indications for testing see pp. 139–140)</td>
<td></td>
</tr>
<tr>
<td>Hormonal Therapy (documentation)</td>
<td>substitution of: recombinant growth hormone, L-thyroxine, hydrocortisone, sex steroids, DDAVP</td>
<td>annually</td>
<td>Form 5, p.160</td>
</tr>
<tr>
<td>QoL</td>
<td>HIT-Leben instruments (see booklet table, p. 62)</td>
<td>annually</td>
<td>questionnaires sent to patients/clinics</td>
</tr>
<tr>
<td>Neuropsychological Diagnostics</td>
<td>for randomized patients ≥ 5y after incomplete resection</td>
<td>preoperative, 3 m post OP and annually</td>
<td>instrument completion and analysis carried out at centers</td>
</tr>
<tr>
<td>Neuroradiology</td>
<td>MRI: pre and post image enhancement, T₁, T₂, CT (if needed) without image enhancement</td>
<td>Every 6–12 m 5–8 y post OP, or more frequently if necessary</td>
<td>for randomized patients: Forms 4 &amp; 7, pp. 159, 162</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>Visual acuity, fundus, field of vision, when appr: colour vision, oculomotor function</td>
<td>min. 1x / year</td>
<td>Form 5, p. 160</td>
</tr>
<tr>
<td>Radiooncology Follow-up care</td>
<td>Follow-up care form: Radiation Therapy – Acute Morbidities</td>
<td>1 x / year</td>
<td>Form 11, p. 166</td>
</tr>
<tr>
<td>Rehabilitation Provisions</td>
<td>Hospital-provided rehabilitation provisions</td>
<td>as needed: every 1–2 years</td>
<td>collaborative studies (see p. 116)</td>
</tr>
</tbody>
</table>
8.2. Rehabilitation

Treatment and rehabilitation of a craniopharyngioma patient requires a multidisciplinary team of pediatric experts in the areas of endocrinology, neuropediatrics, psychology, psychotherapy and physical therapy, and social pedagogy to assess possible endocrine, neuropsychological and ophthalmologic deficits and recovery needs. Especially when dealing with children and adolescents, follow-up care should be long-term and family oriented. Hospitals providing rehabilitation provisions should be institutions that feature specialized experience and a standardized approach to rehabilitating craniopharyngioma patients.

The following measures should be taken into account when preparing rehabilitation care:

<table>
<thead>
<tr>
<th>Provision</th>
<th>Timing</th>
<th>Important considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Emergency medical card</td>
<td>When patient is discharged from hospital</td>
<td>Referrals to support network (see self-help groups category below)</td>
</tr>
<tr>
<td>☐ Information and training of teachers and caregivers</td>
<td>Before patient is discharged from hospital</td>
<td>DDAVP nasal administration for polyuria, oral glucose for hypoglycemia, flexible stress adaptation of hydrocortisone medication (triple dose!)</td>
</tr>
<tr>
<td>☐ Academic psychological diagnostics</td>
<td>as needed</td>
<td>For choosing appropriate school type</td>
</tr>
<tr>
<td>☐ Home schooling</td>
<td>as needed</td>
<td>For applying to responsible educational authority for home schooling</td>
</tr>
<tr>
<td>☐ Medical certificate excusing child from certain types of school sports</td>
<td>When patient is discharged from hospital</td>
<td>As appropriate: excuse from endurance sports, competitive sports, sport instruction without grades. General excuse from school sports is not recommended.</td>
</tr>
<tr>
<td>☐ Self-help groups</td>
<td>as needed</td>
<td>Annual family meeting of craniopharyngioma self-help group. For info. and registration: <a href="http://www.kinderkrebsstiftung.de">www.kinderkrebsstiftung.de</a></td>
</tr>
<tr>
<td>☐ Youth seminars</td>
<td>as needed</td>
<td>Organization for patients &gt; 16 years for supporting transition experiences. For info. and registration: <a href="http://www.kinderkrebsstiftung.de">www.kinderkrebsstiftung.de</a></td>
</tr>
<tr>
<td>☐ Internet homepages</td>
<td>Info. &amp; support contacts</td>
<td><a href="http://www.kraniopharyngeom.de">www.kraniopharyngeom.de</a> <a href="http://www.kinderkrebsstiftung.de">www.kinderkrebsstiftung.de</a></td>
</tr>
<tr>
<td>☐ Acquiring nursing care insurance</td>
<td>as needed</td>
<td>Financial aid for the family and/or outpatient care provisions</td>
</tr>
<tr>
<td>☐ Application for severely disabled person pass</td>
<td>as needed</td>
<td>For income tax exemptions, unemployment support, misc. privileges</td>
</tr>
<tr>
<td>☐ Nutritional counselling</td>
<td>as needed</td>
<td>Lower fat, fiber-rich food sources</td>
</tr>
<tr>
<td>☐ Advanced nutrition psychological diagnostics</td>
<td>as needed</td>
<td>Consultation with study admin. (E-mail: <a href="mailto:kikra.doku@klinikum-oldenburg.de">kikra.doku@klinikum-oldenburg.de</a>)</td>
</tr>
<tr>
<td>☐ Psychotherapy for eating disorders</td>
<td>as needed</td>
<td>Consultation with study admin. (E-mail: <a href="mailto:kikra.doku@klinikum-oldenburg.de">kikra.doku@klinikum-oldenburg.de</a>)</td>
</tr>
<tr>
<td>☐ Physical therapy</td>
<td>as needed</td>
<td></td>
</tr>
<tr>
<td>☐ Rehabilitation provisions</td>
<td>in 1–2 year intervals</td>
<td>Rehabilitation treatment reviewed as appropriate after diagnosis consideration</td>
</tr>
</tbody>
</table>
8.3. Support Organization Addresses

**German self-help group for craniopharyngioma patients**
Internet: http://www.kraniopharyngeom.de

**Deutsche Kinderkrebsstiftung (a German pediatric cancer foundation)**
Adenauer-Allee 134, 53113 Bonn
Tel: +49 (0)228 688460, Fax: +49 (0)228 6884644
E-mail: info@kinderkrebsstiftung.de
Internet: www.kinderkrebsstiftung.de

**Junge-Leute-Seminare (German youth seminars)**
Contact: Frau Frackenpohl, Deutsche Kinderkrebsstiftung
Adenauer-Allee 134, 53113 Bonn
Tel: +49 (0)228 688460, Fax: +49 (0)228 6884644
E-mail: info@kinderkrebsstiftung.de
Internet: www.kinderkrebsstiftung.de
9. Approvals – Medical Ethics Commission and Federal Office for Radiation Protection (BfS)

Approval from the appropriate institutional ethics committee must be sought. Approval for the entire study was obtained from the Ethics Commission of the Medical Faculty at the Julius Maximilians University of Würzburg by the study administration. The Ethics Commission of the Medical Faculty at the Julius Maximilians University of Würzburg audited KRANIOPHARYNGEOM 2007 on the basis of the existing study protocol during their session on 24 July 2006 and delivered a positive decision (see next page). KRANIOPHARYNGEOM 2007 is in accordance with the revised Declaration of Helsinki – 10 October 1975.

Before admitting patients to the study, an information clarification meeting with the parents (and patients if capable of reasoning) must be held in order to fulfil the data acquisition, data processing and data forwarding requirements as well as the written study participation agreement paperwork.

The following points should be covered when informing patients and parents:

- Rather than stipulating therapeutic decisions, the study is designed as a surveillance study where data are collected regarding diagnostics, therapy, and follow-up care for patients after complete resections and patients < 5 years-of-age regardless of resection grade.
- Randomisation is carried out after an incomplete craniopharyngioma resection for patients ≥ 5 years regarding timing of postoperative irradiation once written agreement from parents (and patients if capable of reasoning) has been acquired.
- Permission is requested for electronic data processing of patient information.
- The patient is guaranteed that there are no treatment disadvantages from rejecting participation.
- Extracted tumor material, blood, CSF and cyst fluid will be used for scientific purposes.

The above information is contained in the information brochure for parents/patients. However, the information brochure does not replace the personal clarification meeting with parents and patient.

A separate clarification meeting must be held with each and every diagnostic and therapy discipline (neurosurgeon, radiation therapist, endocrinologist, and neuroradiologist) regarding the specific benefits and risks of the proposed diagnostic and therapeutic measures.

9.1. Approval from Federal Office for Radiation Protection (Bundesamt für Strahlenschutz / BfS)

KRANIOPHARYNGEOM 2007 has no plans to deploy any new radiation treatment. Randomization is solely concerned with the timing of when postoperative irradiation is performed. In medical science terms, deployment of radiation therapy in both randomization arms conforms to typical irradiation modalities approved for and available to patients with a residual craniopharyngioma tumor remnant after incomplete resection.

In context of the "references to application for permission to use radioactive materials or ionizing radiation on people in medical research according to § 23 StrlSchV" (paragraph 23 of radiation protections V):

II (1): The distinction inherent in medicine and as stated in §23 of StrlSchV, permission-requiring use of radioactive materials or ionizing radiation in clinical conditions poses difficulties in individual cases. An important criterion accompanying the question is whether use of the radioactive materials or ionizing radiation is procedurally and magnitude-wise routinely executed in a contextually patient medical-treatment manner conforming to the research intent regarding the relevant disease. If this is not the case, use of radioactive materials or ionizing radiation is contingent upon further official review and approval according to §232 StrlSchV.
9.2. Approval – Ethics Commission, Medical Faculty at Julius Maximilians University of Würzburg, 24.07.2006

Ethik-Kommission der Medizinischen Fakultät der Universität Würzburg

Herrn
PD Dr. med. Hermann Müller
Direktor des Zentrums für Kinder- und Jugendmedizin
Klinikum Odenburg gGmbH
Dr. -Eden-Straße 10
26133 Oldenburg

97080 Würzburg
Josef-Schneider-Straße 2, D7
Telefon (0931) 201 53856
Telefax (0931) 201 53860
E-Mail: Schmidt_S1@klinik.uni-wuerzburg.de

Bearbeitungsnummer: 94/06
Wö/Schm Würzburg, den 26.07.2006
(bei Rückfragen immer angeben)

Studie: Kraniofaryngeom 2007 - Multizentrische, prospektive Bobachtungsstudie von Kindern und Jugendlichen mit Kraniofaryngeom

Sehr geehrter Herr Doktor Müller,

in der Sitzung der Ethik-Kommission vom 24.07.2006 wurde o. g. Studie auf der Basis folgender Unterlagen beraten:
- Antrag vom 04.07.2006
- Votum der Ethik-Kommission der Medizinischen Fakultät der Universität Würzburg vom 22.11.1999 zur Studie 140/99
- Aufklärungsbogen für Erziehungsberechtigte und Patienten vom 06.06.06
- Folgeantrag an die Deutsche Krebshilfe vom Juni 2006
- Studienprotokoll Kraniofaryngeome 2007 vom 06.06.06


Sie werden gebeten, der Ethik-Kommission das Studienende anzuzeigen.


Entsprechend der ausschließlich beratenden Funktion der Ethik-Kommission betrifft unser Votum nur die ethische Beurteilung des Projektes. Die ärztliche und juristische Verantwortung verbleibt jedoch uneingeschränkt beim Projektleiter und seinen Mitarbeitern, so dass alle zivil- und haftrechtlichen Folgen, die sich ergeben könnten, von dieser Seite zu tragen sind.

Die Ethik-Kommission wünscht Ihnen für Ihr Vorhaben viel Erfolg.

Mit freundlichen Grüßen

i. V. [Unterschrift]

Prof. Dr. F. Grehn
Vorsitzender der Ethik-Kommission
9.3. Permit from Federal Office for Radiation Protection (BfS) 31.08.2006

Datum und Zeichen Ihres Schreibens:  Mein Zeichen:  Durchwahl:  Datum:
SG21-22461-1-2006-014  1413  31.08.2006

Genehmigungsbedürftige Anwendung radioaktiver Stoffe oder ionisierender Strahlung am Menschen in der medizinischen Forschung gemäß §§ 23 und 24 StrSchV

Betreff: Klinische Studie: Kraniopharyngeom 2007
Prospective, multizentrische Beobachtungsstudie von Kindern und Jugendlichen mit Kraniopharyngeom

Bezug: Ihre Schreiben vom 10.07.2006 (PD Dr. Müller) mit Studienprotokoll und vom 01.08.2006 und 21.08.2006 inklusive Bestätigungen der Leitlinienkommissionsmitglieder

Sehr geehrter Herr PD Dr. Müller,

aufgrund der o.g. eingereichten Unterlagen stelle ich fest, dass eine Genehmigungsbedürftigkeit für folgende von Ihnen vorgesehene Anwendung ionisierender Strahlung im Rahmen der o.g. Studie nach §§ 23 und 24 StrSchV nicht besteht:

Art der Strahlentherapie:

Die Kosten meiner Prüfung haben Sie zu tragen.
Die Kostenfestsetzung erfolgt mit gesondertem Bescheid.
Begründung:

Nach § 23 StrlSchV bedarf derjenige einer Genehmigung, der zum Zwecke der medizinischen Forschung radioaktive Stoffe oder ionisierende Strahlung am Menschen anwendet.

Der Begriff der medizinischen Forschung ist in § 3 Abs. 2 Nr. 14 StrlSchV definiert. Danach müssen zwei Voraussetzungen erfüllt sein, damit eine medizinische Forschung vorliegt. Die Anwendung von radioaktiven Stoffen / ionisierender Strahlung

- dient der Fortentwicklung der Heilkunde oder der medizinischen Wissenschaft und
- dient nicht in erster Linie der Untersuchung oder Behandlung des einzelnen Patienten.

Die Abgrenzung zwischen Heilkunde und genehmigungsbefugter Anwendung ionisierender Strahlung im Rahmen der medizinischen Forschung gemäß § 23 StrlSchV kann im Einzelfall Schwierigkeiten bereiten. Ein wichtiges Kriterium ist dabei u.a. die Frage, ob die Anwendung von ionisierender Strahlung nach Art und Umfang dem entspricht, was im Rahmen der Heilkunde bei Patienten mit der für das Forschungsvorhaben relevanten Erkrankung in typischer Weise durchgeführt wird. In diesem Fall ist die Anwendung von ionisierender Strahlung nicht als genehmigungsbefugte Forschung gemäß § 23 StrlSchV einzustufen.

Bezüglich Ihres Vorhabens ergibt sich Folgendes:

1. Im Schreiben vom 10.07.2006 mit dem Studienprotokoll in der Anlage wird nachvollziehbar dargelegt, dass bei Kindern und jugendlichen Patienten, die an einem Kranioopharyngeom erkrankt sind und bei denen nur eine inkomplette Resektion erfolgen konnte, die klinische Indikation für eine Strahlentherapie besteht. Dies entspricht dem derzeitigen Stand der Heilkunde bei dieser Diagnose.


3. In der o.g. Studie sollen die Wirksamkeit und Sicherheit einer Strahlentherapie bei Patienten ≥5 Jahren, deren Kranioopharyngeom inkomplett reseziert wurde, hinsichtlich des Zeitpunktes der postoperativen Bestrahlung untersucht werden. Es werden zwei Therapiestrategien, die z. Bt. in der Heilkunde bei der postoperativen Strahlentherapie des inkomplett resezierten Kranioopharyngeoms bei Kindern und Jugendlichen angewandt werden, verglichen.


4. Angewandt wird eine 3-dimensionale Konformationstechnik mit Stehfeldern, die Einzeldosis beträgt 1,8 Gy, 1 x tägl., 5 x wöchentlich. Die Gesamtdosis beträgt 50,4 – 54 Gy. Es erfolgt eine Randomisierung in zwei Arme: Behandlungsarm I:

Strahlentherapie innerhalb von 3 Monaten nach der Operation
Behandlungsarm II:
Beginn der Strahlentherapie bei Nachweis der Progression im MRT (MRT-Nachkontrollen bei o.g. Patienten in 3-monatigen Abständen).


Fazit:

Unter Berücksichtigung der Darlegungen in Punkt 1-5 erfolgt o.g. Strahlentherapie in erster Linie zur Behandlung im Rahmen der Heilkunde und nicht zum Zweck der medizinischen Forschung. Ein Antrag auf Genehmigung zur Anwendung von ionisierender Strahlung am Menschen in der medizinischen Forschung gemäß § 23 und § 24 StrlSchV ist somit nicht zu stellen.

Die Entscheidung über die Kosten erfolgt gemäß § 21 Abs. 1 Nr. 4 Atomgesetz in Verbindung mit § 23 Abs. 2 StrlSchV und den §§ 1 und 2 Satz 1 Nr. 6 der Kostenverordnung zum Atomgesetz (AtKostV). Ihre Kostenpflicht - als Veranlasser dieser Prüfung - ergibt sich aus § 1 Satz 2 AtKostV in Verbindung mit § 13 Abs. 1 Nr. 1 Verwaltungskostengesetz (VwKostG).

Rechtsbehelfsbelehrung:


Mit freundlichem Gruß

Im Auftrag

[Unterschrift]

Dr. B. Goetze
Supplements

10. Literature


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11. Information Sheet for Legal Guardians and Patients:

Prospective, multicenter study of children and adolescents with craniopharyngioma – KRANIOPHARYNGEOM 2007

Director of studies: Prof. Dr. med. Hermann Müller, Klinik für Allgemeine Kinderheilkunde, Hämatologie / Onkologie, Zentrum für Kinder- und Jugendmedizin, Klinikum Oldenburg gGmbH, Rahel-Straus-Str. 10, 26133 Oldenburg; Germany. Tel.: +49 441 403-2072, Fax: +49 441 403-2789, E-mail: kikra.doku@klinikum-oldenburg.de

Patient: born on

Your child was diagnosed with craniopharyngioma. Craniopharyngioma is a dysmorphia coming from tissue, which in its development was already disrupted embryonally, that is, even before birth. The reasons for this malfunction are so far unknown. The tumor visible on magnetic resonance scans is therefore no malignant neoplasm but rather a type of dysmorphia. However the craniopharyngioma lies in direct proximity to brain structures that are very important for physical and mental development. The proximity to the optic nerves can lead to vision impairments and even to vision loss. Adjacent brain structures such as the pituitary gland and the hypothalamus are responsible for the formation of many hormones which, in turn, are responsible for growth, weight regulation, puberty development and fluid balance. The first ailments of patients often manifest in deficiencies in this hormones, which are caused by the craniopharyngioma. In addition, proteins in the brain build up in direct proximity to the craniopharyngioma and these play an important role in the day-night rhythm, the ability to concentrate and the eating behaviour of patients.

The treatment of a child or adolescent with newly diagnosed craniopharyngioma is most often surgery. Your physician/neurosurgeon will speak to you about the surgical procedure (how and how much should one operate/removed). You will be informed that the craniopharyngioma often cannot be completely removed because otherwise major damage could be done to adjacent brain structures. On the other hand, there are also craniopharyngiomas that reappear in spite of complete removal. If parts of the craniopharyngioma cannot be removed surgically, radiation therapy after the operation must be contemplated.

Except for a few cases where the pituitary gland (pituitary body and pituitary stalk) was not be removed, after the operation you/your child will have to take hormones in the form of pills, nasal drops or subcutaneous injections regularly and for life. About half of all patients with craniopharyngioma become significantly overweight after treatment. Visual disturbances existing before the operation often do not improve. Craniopharyngioma patients present with impairments of memory and alertness.

Since it is so far unclear as to what extent treatment of patients prevents or possibly even reinforces the above secondary illnesses, we collect data on treatment and health after completion of therapy. The objective of our study is to determine what form of treatment is the most effective and simultaneously the gentlest for children and adolescents with this illness. We wish to collect and analyze data on diagnostics, therapy and postoperative care. We request your written approval for data processing using a special form. To get this information about post-treatment health and condition, regular follow-up examinations are needed. These follow-up examinations are done for all patients three months after surgery/treatment and then in annual intervals in the clinic in their hometown. The follow-up examinations include:

- physical examination and height/weight measurements,
- magnetic resonance scans of the head,
- examination by an ophthalmologist,
- tests / questionnaires about mental development, ability to concentrate, eating behaviour and health-related quality of life (you will receive appropriate questionnaires every year or will be given them by your attending physician with the request to fill them out and return them to the study secretary).
- neuropsychological examinations will be carried out annually in the attending clinic,
- blood tests to determine hormone levels
If your child's craniopharyngioma could only be partially removed and your child was 5 years old or older at operation, we would like to recommend a special treatment to you. For information about this, please refer to our special explanatory sheet on the following pages.

The responsible (neuro-) radiologist will inform you about the possible risks of the use of contrast agents during MRI. Bone age and body composition is determined by means of minor radiation exposure. We recommend the body composition test using DEXA for patients who become distinctly overweight after surgery. The body composition test involves minor radiation exposure that is more or less comparable to that of a hand X-ray. Bone age is determined annually using an X-ray of the left hand. Determining bone age is important to assess the physical development and growth of your child and to promptly identify and treat any disorders that might occur. All these tests do not involve pain.

The relationships between the often imminent obesity and craniopharyngioma are only inadequately known. The treatment of obesity is very difficult. In order to better understand the relationships and perhaps even to offer treatment options in the future, we wish to study a part of the surgically removed craniopharyngioma tissue or tapped cystic fluid and simultaneously extracted blood samples for factors which could be responsible for obesity.

The analysis will be done under full protection of patient/physician confidentiality and data protection. Your consent to the data processing is voluntary. In case you refuse to participate, you or your child will not suffer any disadvantage. You can cancel your consent at any time.

Date: ..........................................................  
Person responsible for care and custody

Date: ..........................................................  
Patient

Date: ..........................................................  
Discussing physician

Date: ..........................................................  
Witness
Your child was diagnosed with craniopharyngioma. Craniopharyngioma is a dysmorphia coming from tissue, which in its development was already disrupted embryonally, that is, even before birth. The reasons for this malfunction are so far unknown. The tumor visible on magnetic resonance scans is therefore no malignant neoplasm but rather a type of dysmorphia. However, the craniopharyngioma lies in direct proximity to brain structures that are very important for physical and mental development. The proximity to the optic nerves can lead to vision impairments and even to vision loss. Adjacent brain structures such as the pituitary gland and the hypothalamus are responsible for the formation of many hormones which, in turn, are responsible for growth, weight regulation, pubertal development and fluid balance. The first complaints and symptoms of patients often manifest in deficiencies of this hormones, which are caused by the craniopharyngioma. In addition, proteins in the brain build up in direct proximity to the craniopharyngioma and these play an important role in the day-night rhythm, the ability to concentrate and the eating behaviour of patients.

The treatment of a child or adolescent with newly diagnosed craniopharyngioma is most often surgery. The neurosurgeon who operated on you/your child decided with full responsibility during the operation which surgical procedure (how and how much should one operate/removed) to take. At first it seems disappointing that your/your child's craniopharyngioma could not be completely removed surgically. However, we know from studies that complete removal can often injure adjacent brain tissue, leading to secondary illnesses for which there is no effective treatment available. In this respect the craniopharyngioma was partially removed to prevent these secondary illnesses caused by surgically related injuries.

If parts of the craniopharyngioma cannot be removed surgically, another operation, radiation therapy or further waiting must be contemplated. Undergoing another operation entails a high risk since the initial operation produces scars which make it more difficult for the surgeon to achieve complete removal in another operation. Radiation therapy offers the possibility to prevent further growth of the residual tumor as effectively as possible. The advantage of the wait-and-see approach is that a decision on treatment can/must be made only if the residual tumor grows further.

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**What does the still existing residual tumor of the craniopharyngioma mean for the future health and development of your child?**

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**Which treatment is now recommended in case of a residual tumor?**
This question cannot be definitively answered based on our know-how today and the results of prior studies. The advantage of radiation therapy of the residual tumor performed directly after the first operation would be that further tumor growth and hence more operations are avoided. It was observed that patients with serious long-term consequences and concomitant diseases had undergone more surgeries than patients who hardly suffered any secondary illnesses. In case of tumor growth radiation would be the most important treatment option.

On the other hand, craniopharyngioma is a dysmorphia and not a malignant cancer. In this respect, it is difficult to foresee whether the residual tumor will grow (again) in the future. In scientific literature the long-term probability of growth of the residual tumor is indicated to be between 80% and 100%. In our own studies we have observed growth of the residual tumor within the first four years after surgery in half of our patients.

**What would we recommend to you with regard to further therapy?**

We would like to suggest that you carry out a random study of the issue of the time appropriate for radiation therapy in case of the existence of a residual tumor after surgery. What does randomization mean for you/your child and further therapy? Since we cannot give you a well-founded recommendation on whether it would be better to undergo radiation therapy immediately after an incomplete operation or only if the residual tumor grows further, we would like to examine this issue scientifically. In this randomized study, as is customary in all other tumor diseases and with your approval, we would decide by random whether to perform irradiation immediately (3 months) after surgery or at the time, when the residual tumor grows again. Only in this manner and with your help for several years can we answer the question of which time period is optimal for radiation therapy of a residual tumor after incomplete operation of the craniopharyngioma. The random decision applies to the time period when radiation therapy of the residual tumor is performed. The radiation therapy to be performed in case of residual tumor is a recognized and effective therapy which can prevent secondary illnesses. The time when this effective therapy should be applied is so far unclear and would have to be determined randomly.

For patients who are randomized into the group with early radiation therapy after surgery there is the possibility that radiation is carried out also in those cases where no growth of the residual tumor occurs. However, studies have shown that this happens in the long term only in less than 10% of patients. The small risk that radiation is performed in a few cases which afterwards would prove unnecessary must be weighed against the risk that late radiation or surgery in case of tumor growth can result in a more extensive therapy with possible negative effects on health and chances of healing.

**What are the advantages of randomization for your child and for the scientific study?**

The randomization, that is, the random decision with regard to the time of radiation therapy for you/your child after incomplete removal of the craniopharyngioma has no disadvantage in view of the current state of know-how based on international studies. No one knows which time would be optimal for radiation therapy in order to prevent secondary illnesses. Past studies indicate that the quality of life of craniopharyngioma patients who underwent radiation is not lower than that of patients who did not undergo radiation. To find out which time would be the best to perform the necessary radiation, a random decision for the scientific study is necessary. Only based on the results of such a study, it is possible to give a recommendation with regard to the timing of radiation.

In case you/your child are randomized in the therapeutic arm undergoing radiation directly after surgery, it is ensured that the planning and execution of the radiation is assessed and checked by a reference center so that the radiation therapy meets the highest quality standard. The same quality standard and appraisal by the reference center for radiation therapy is ensured if you/your child are/is randomized in the treatment arm undergoing later radiation.
Are there disadvantages with regard to the treatment for your child that arise from the randomization?

There are no disadvantages for you/your child with regard to treatment in case of participation in the randomization!

If you have further questions about the planned randomization, we will be glad to answer them.

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Date: ........................ Person responsible for care and custody
Date: ........................ Patient
Date: ........................ Discussing physician
Date: ........................ Witness
PATIENTS AGE 5 YEARS OR OLDER AFTER INCOMPLETE RESECTION
Information sheet on randomization for patients 7 - 13 years:

Prospective, multicenter study of children and adolescents with craniopharyngioma – KRANIOPHARYNGEOM 2007
Director of studies: Prof. Dr. med. Hermann Müller, Klinik für Allgemeine Kinderheilkunde, Hämatologie/ Onkologie, Zentrum für Kinder- und Jugendmedizin, Klinikum Oldenburg gGmbH, Rahel-Straus-Str.10, 26133 Oldenburg, Germany. Tel.: +49 441 403-2072, Fax: +49 441 403-2789, E-mail: kikra.doku@klinikum-oldenburg.de

Patient: born on

Dear patient,

You are aware that you have a tumor (tissue that does not belong) that is called craniopharyngioma. That is a difficult word. For this reason, let us just call craniopharyngioma cranio, following the example of most patients. Cranio is not cancer and therefore does not have the malignant properties of cancerous tumors. We still do not know why the cranio appears. But it is sure that neither you nor anyone else has done anything wrong which then led to the appearance of the cranio. Cranio is a dysmorphia that probably appears very early and in some cases even before birth. Cranio is a very rare disease. In Germany about 30 children and adolescents suffer from it every year.

All the same we must treat cranio as a very serious disease. Cranio is located in the head behind the eyes at a place where many important parts of the brain are located. In direct proximity to the cranio is the optic nerve which allows you to see. The pituitary gland is also right beside the cranio. This gland produces hormones which you need to grow, pass puberty and have enough energy to be fit. You might already have had such ailments before the cranio was detected. This was probably because the cranio has grown and was pressing on the gland and the optic nerve.

Cranio "unfortunately" could not be completely removed during the operation.

During the operation it was impossible to remove the cranio completely. At first that was surely a disappointment for you and your parents. But you must be aware that it would be too dangerous to completely cut out the cranio. Because there are many important organs beside the cranio, one must be extremely careful when operating in order not to damage anything in the surrounding area. If the cranio grew in the proximity, one cannot cut out the cranio completely without injuring important organs that lie nearby. We hope that you understand that one cannot completely remove the cranio for this reason because everyone is wishing that you get better after the operation.

What happens now with the rest of the cranio?

To begin with, it is important that you recover well from the operation. But we must already think about what will happen to the rest of the cranio. We have seen in other patients that the rest of the cranio often begins to grow again. That is why it is important to sit down with you, your parents and the doctors and think about what we should do next.

If some of the cranio still remains after the operation, then we can again try to operate. Another operation is often not simple. After the first operation scars appear beside the cranio and they make it more difficult to completely remove the neoplasm in the second attempt. We can also treat the rest of the cranio with radiation without having to operate again. In radiation treatment X-rays are directed at the remaining cranio from an external source.

The rays destroy the tissue of the cranio. You probably know a similar situation involving X-rays or CT scan which is done to produce images.
In case of radiation the X-rays have a much higher dose so that the irradiated remainder can no longer grow afterwards. During radiation therapy you actually have to remain still only for a minute and should not move. However, the radiation therapy lasts approximately 5-6 weeks, with one radiation session per day. Only the residual cranio is irradiated.

### When should we start radiation treatment?

No one knows exactly when is the best time to treat the rest of the cranio with radiation. Some say it is better to treat it soon so that the rest does not grow again. We know that waiting too long and possible further operations are not too good for your health. Another possibility would be to wait until the rest of the cranio grows again and then start radiation therapy. Nobody knows at the moment what the better decision is. This is why it would also be too much if you have to make the decision.

### Our recommendation

Since there are no definite experiences on when the best time would be, we would let the contingency decide. We make such a random decision (also called randomization) so that we can better know in the future when the best time period would be. At any rate, the radiation treatment is the same and is done similarly well in both cases. We would only decide when they will take place. Either we decide that radiation treatment is started relatively soon (4 months) after the last operation or radiation therapy is started only later after new scans are received showing growth of the residual cranio.

### Are there advantages or disadvantages?

No. There are no advantages or disadvantages. It does not matter how the decision to begin radiation therapy is made.

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*If you have more questions, please contact your doctors or contact me by telephone, fax or e-mail:*

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12. Collaborative studies

12.1. Disturbances of epigenetic regulation in the origins of craniopharyngioma

Prof. Dr. Michael Frühwald, Ph.D.
University Hospital Münster, Pediatric Hematology and Oncology, Germany

Craniopharyngiomas constitute 5% of all CNS tumors in children and adolescents. It is the fourth most commonly diagnosed CNS tumor in children following astrocytic, medulloblastoma and ependymoma tumors. Unlike these other types of childhood tumors, little is known regarding the genetic basis of this tumor group. Craniopharyngioma screening analysis using zytogenetic methods was able to prove abnormalities in chromosomes 2 and 12. Genloci have not yet been identified. A study of mutations in the tumor suppressor gene TP53 revealed only normal attributes of this gene. Histogenically, craniopharyngiomas are derivatives of remnants of Rathke's pouch. These deviations of a normal embryo genetic development play an important adeno- and neurohypophysis role in the origin of craniopharyngiomas. Several teams have been able to prove that the differentiation and specification of precursor cells of the CNS epigenetic mechanism, e.g. DNA methylation and histone deacetylation, underlie this phenomenon. We and other teams were able to show that epigenetic variations in certain CNS tumors are a frequently occurring phenomenon (1, 2). The analysis of deviating DNA methylation in craniopharyngiomas could contribute to a better understanding the causes of these tumors. Both prognostic and therapeutic clinical relevance of epigenetic mutations can be attained. Methylation gene patterns could be prognostic indications of a number of different tumors (3). Both histone deacetylase inhibitors and DNA methyl transferation are in phase I and II studies with therapy resistant malignoma patients, as well as in benign mutations such as sickle cell anemia.

The hypothesis that deviating methylation plays a role in the origin of craniopharyngiomas will be tested by screening of craniopharyngioma paraffin tissues. Under microdissection of representative tumor samples, candidate genes have been examined using methylation-specific PCR and quantitative COBRA (Combined Bisulfite Restriction Analysis) in collaboration with PD Dr. Hasselblatt at the Institute of Neuropathology, Münster. Well-known methylation target genes such as tumor suppressors RASSF1A and p16\(^{INK4A}\) belong to these candidate genes and also genes that play a role in pituitary development. After an initial screening, expressions of relevant genes are examined under microdissection of primary tumor material. Incorporating molecular finds in clinical contexts achieves a narrow correlation with the study databases (e.g. prognostics and potential therapy for incomplete resected tumors).

Analysis of epigenetic mutations promises insights into molecular pathogenisis of craniopharyngiomas and with a better understanding of these processes, ultimately improvements in the clinical care of craniopharyngioma patients can be expected.

References


Collaborative studies

12.2. Tumor suppressors and oncogenes in craniopharyngioma
Prof. Dr. Willem Kamps, Prof. Dr. Evelyn de Bont, University Hospital Groningen, Netherlands

In this proposal we formulate the following goals:
1. To find and characterize potential tumor suppressor genes and/or oncogenes in areas of chromosomal aberrations.
2. To integrate the candidate genes (in chromosomal losses and/or gains) with the results of proteomics and results of the kinomics (kinase array) to obtain insight in the involved pathways to ultimately find new biological treatment strategies.

Plan of investigation
We will start with array comparative genomic hybridisation (array CGH) patient craniopharyngioma tissue samples in close collaboration UMCG and Klinikun Oldenburg. With this method we will be able to identify areas with consistent, recurrent chromosomal aberrations in craniopharyngioma. Moreover, proteomics and kinomics will demonstrate specific activated proteins related to chromosomal losses and gains. The unique combination of array CGH, proteomics and kinomics will lead to a direct insight in biological processes in craniopharyngioma tissues. By pathway analysis we will be able to relate these candidate genes (found by array CGH) to signalling pathways (found by proteomics and kinomics). We will link our results to biological inhibitors of signalling pathways. At this specific moment pharmaceutical industries have an increased interest and availability of biological inhibitors of signalling pathways. When interesting chromosomal targets are identified a FISH technique can help to identify the specific marker in a larger number of patient samples while paraffin embedded tissue can be used.

So, it will be clear that defining chromosomal aberrations AND protein levels AND tyrosine kinase activity in identical craniopharyngioma tissues will lead to better understanding of the crucial events in ontogenesis, biological behaviour, therapy response as well as will help to design more rationale refined treatment strategies for (subgroups of) children with craniopharyngioma.

Samples/Patients
Patient samples: preferably fresh-frozen tissue samples for array CGH, proteomics and kinomics (n=10-15). In the near future it seems that array CGH on paraffin embedded material will be possible (easier available). For all these patients, clinical data including treatment, late effects, follow up and survival data are available from Oldenburg. New in this proposal is the integration of array CGH analysis (UMCG) and proteomics (UMCN) with kinase array results.

Methods
Array CGH: The whole genome array contains ~7000 clones (BAC/PAC libraries) of Dr P de Jong and the Sanger Institute resulting in a resolution of 0.5 MB as described in more detail by Kok (K. Kok et al, 2005). DNA of craniopharyngioma tissue will be compared with normal reference DNA thereby identifying areas of gains and losses.

Proteomics: 2D gel electrophoresis combined with Surface Enhanced Laser Desorption ionization and Time of Flight (SELDI-TOF) and Matrix-Assisted Laser Desorption / Ionization Time-Of-Flight Mass Spectroscopy (MALDI-TOF MS). LTQ Fourier Transform Ion Cyclotron Resonance Mass spectrometer (FTMS). (studies performed at University Medical Center St Radboud, Nijmegen; Dr. LP van den Heuvel; Dr. JL Loeffen).

Kinomics: whole genome kinome array of Prof M Peppelenbosch (UMCG) will be used.

Statistics
Array CGH: To determine significant DNA copy number changes in the tumor compared to the reference DNA, the software program Bluefuse (Bluegnome ltd, Cambridge) will be used. Common regions of loss or amplification will be selected using, the software program CGH miner.

Proteomics and Kinomics will be analyzed only as (activated) proteins related to specific chromosomal gains and losses.
Collaborative studies

12.3. Profiles of Angiogenesis in craniopharyngioma
Prof. Dr. Willem Kamps, Prof. Dr. Evelyn de Bont, University Hospital Groningen, Netherlands

Purpose:
To investigate the angiogenic profile in craniopharyngioma as a possible future target for risk assessment.

Methods and Statistics:
From representative small areas in biopsies of formalin-fixed, paraffin-embedded tumor tissue blocks, a tissue micro array (TMA) consisting of at least three representative 0.6 mm cores will be constructed. This technique is available in the department of pathology (in collaboration with Dr W den Dunnen) at the UMCG. TMAs are a significant advance over previous attempts to put multiple samples in a single paraffin block or even to use one slide for each individual tumor for staining. There are many potential benefits of using TMAs. For instance, the ability to screen large numbers of cases in a single staining run, thereby minimizing run-to-run variability in immunohistochemical staining. They dramatically decrease costs of conducting immunohistochemical studies and increase numbers of studies that can be performed on small pieces of tissue, by using small cores of tissue rather than cutting sections of every block for each study.

Immunohistochemical staining will be assessed for VEGF A, B, C, D, VEGF Receptors 1 and 2 and neuropilin-1 receptor and phosphorylation specific antibodies will be used for VEGFR-2. To address the question whether tumor cells are positive or selected cell subpopulations such as endothelial cells, larger conventional slides will be stained in a selected number of cases. In these conventional staining vessel density can be measured. Moreover, information regarding vessel morphology will be gained by staining for FVIII-related antigen, collagen for the basal membrane, and anti smooth muscle actin, desmin and PDGFR beta for pericycle coverage.

Correlations between staining results of the individual samples in TMA blocks will be accessible by the created worksheet with univariate and multivariate analyses (Liu et al 2002). Even with hierarchical clustering analysis we will be able to assess relatedness within groups of craniopharyngioma based on their immunostaining.

The results will be correlated to clinical relevant parameters. Meaningful profiles will then be available in the future to stratify patients to specific targeted therapies.

Patient samples: paraffine embedded material of patient craniopharyngioma samples. Preferably 80-100 when TMA blocks can be used. For all these patients, clinical data including treatment, late effects, follow up and survival data are available from Oldenburg.
Craniopharyngiomas are the most commonly occurring non-neuroepithelial tumors in children. The craniopharyngiomas found in children are usually adamantinous while the papillary histological variant occurs more often in adults.

For years hardly any data existed regarding the molecular pathogenics of craniopharyngiomas. Then isolated cytogenetic analyses revealed abnormalities of chromosomes 2 and 12. In 2002, Sekine et al. described for the first time frequent mutations in the β-catenin for the craniopharyngioma adamantinomatous subtype leading to an activation of the Wnt signalling pathway. This signalling pathway is highly preserved during embryonic development. Oncogenic mutations were identified in different neoplasms (e.g. in hepatoblastoma, Koch et al., 1999) – a phenomena confirmed in studies by Kato et al. and Buslei et al. For the first time a signalling pathway associated with the origin of these tumors was identified. It was later found that mutations involving phosphorylation sites at the N-terminal domain of proteins are responsible for successful dismantling of the protein. Mutated proteins become stabilized and effect oncogenes. The mutations pertain to different amino acids and their occurrence and type are possibly associated with the different histological features of craniopharyngiomas (Kato et al., 2004).

The goal of this investigation is to assess the mutation status of β-catenin and the activation of the Wnt signalling pathway in a larger collective, then correlating this with histological as well as clinical patient data.

Paraffin-embedded material will be histologically characterized along with immunohistochemical reactions to cytokeratin and Ki-67. Thin tissue sections will be extracted using laser capture microdissection enabling examination of genomic DNA from epithelial tumor cells and β-catenin mutations (especially exon 3) using amplification and sequencing. In the absence of mutations, an analysis of the β-catenin protein complex components (Axin-1, Axin-2, and APC) will be performed. Activity of the signalling pathway will be characterized by immunohistochemical representation of β-catenin nuclear localization and by other archived, deep-frozen material through quantifications of specified target genes (DKK-1, AXIN-2) using real-time PCR (Koch et al. 2005).

Afterwards, correlation of occurrence and mutation type and/or activation of the signalling pathway with histological parameters (e.g. proliferation) and course parameters will be analyzed using appropriate statistical procedures. These investigations can cover a representative collective of possible diagnostic and prognostic significances of activated Wnt signalling pathways in craniopharyngiomas.

This makes this investigation of the Wnt signalling pathway particularly interesting because it portrays a possible therapeutic target in these tumors through newly identified low molecular substances.

References:


Patient information:

Last name: ..............................................................
First name: ............................................................
Date of birth: ............................................................
Sex: [ ] f [ ] m
Surgery date: ...........................................................

Diagnosis: ..........................................................................................................................................

[ ] Initial diagnosis [ ] relapse [ ] post irradiation

Therapy study: ..............................................................
Remarks (e.g. 2nd relapse):

............................................................................................................................................................
............................................................................................................................................................

Examination material:

Please mark as applicable:

0 tumor specimen .............................................
0 aspirated cyst fluid: .................................
0 aspirated CSF: ..............................................
0 tumor swab preparations ............................
0 blood (green Monovette) for DNA extraction
0 blood (Monovette collection tubes) for leucocytes isolation from serum
0 serum .............................................................
0 normal tissue ..............................................
0 other: .............................................................

Extraction date: ..............................................................

Localization:

Contact partner (+ Telephone no.): ..............................................................

Address:
Prof. Dr. T. Pietsch
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Guide for tumor material repository submission

**IMPORTANT:** always work with sterile gloves, scalpel, anatomical tweezers, etc. to protect tissue from RNase contamination and to maintain general sterility.

**1. Procedure for resectable tumors**

The pathologist should remove and divide tumor specimen (resection edges, any noticed necrosis, cystic and solid components are always archived in addition to tumor specimens). Take at least two specimens A and B (more if possible: C, D ca. 1 cm³ each). Divide both A and B into 4 portions as follows: A1, A2, A3, A4 and B1, B2, B3, B4. Any remaining tumor tissue goes to the local pathologist for diagnostics.

A2, A3 and A4: freeze in liquid nitrogen.

A1: produce 10 swabbed cell preparations for FISH assay, putting portion into 4% formalin solution afterwards for histology assessment. Label swabbed preparations and air dry.

Repeat A1 process with B1, B2, B3 and B4 portions.

If pathologist does not need all remaining tumor tissue from large surgical preparations for diagnostics, cut remaining remaining tumor tissue into small slices, freeze and submit in 50 ml collection tubes. *The pathologist decides which additional tumor tissue can be frozen!*

**2. Procedure for non-resectable tumors**

Tumor tissue distribution depends on size of biopsy and should be performed by the pathologist. If possible, the surgeon should remove specimens from 2 different tumor areas (each ca. 1 cm³). Depending on the biopsy size, a portion should be removed for histological diagnostics and remaining tumor tissue deep frozen in liquid nitrogen (see above). In smaller biopsies, the pathologist decides what should transpire and how much tissue can be frozen.

**Directions for freezing in liquid nitrogen**

- Fill 50 ml vial with liquid nitrogen.
- Label several 1.8 ml (RED) collection tubes with name, date of birth, localization (A, B), OP date), unscrew and precool unseeded liquid nitrogen.
- Cut tumor specimen into smaller portions to fit into the 1.8 ml collection tubes.
- Shock freeze by dropping into liquid nitrogen (DO NOT submerge into nitrogen with tweezers and DO NOT let pieces stick to container wall!).
- Remove 1.8 ml tubes from liquid nitrogen (NO liquid nitrogen should remain in tubes!).
- Transfer and seal frozen portions into 1.8 ml collection tubes. Note time.
- Keep sealed tubes with tumor portions in liquid nitrogen.
- If required: Store at –70 to –80° C until delivery.

**Comparison blood and normal tissue**

Drop 5–10 ml peripheral blood into citrate-treated Monovette collection tube (green stopper) and freeze in liquid nitrogen. Fill 4 ml blood in glass Monovette collection tube (blue-black stopper). DO NOT freeze – send unfrozen in tumor box lid. Cut comparison tissue into smaller portions if necessary and freeze in liquid nitrogen in 1.8 ml collection tubes (GREEN).

**Shipping**

Express shipping of deep-frozen tumor portions in 1.8 ml collection tubes, normal tissue, and citrate blood on dry ice in the tumor box®. Tumor box chamber should be completely filled with dry ice. Ship swabbed cell preparations and glass Monovette in the lid of the tumor box at 4° C.
Instructions for archiving tumor sample

A. Required material

1. These instructions
2. Tumor specimen kit:
   - 20 Superfrost microscope slides for tumor cell swab preparations
   - 5 microscope slide boxes
   - 1 50 ml collection tube for handling liquid nitrogen
   - 7 1.8 ml collection tubes for deep freezing fresh tissue
     (6 x RED for tumor portions, 1 x GREEN for normal tissue)
   - 1 5 ml Monovette collection tube containing citrate for comparison blood (DNA extraction)
   - 1 4 ml glass Monovette collection tube (blue-black stopper) for leucocytes isolation
   - 1 submission form
3. Pencil and fine-tipped permanent marker for labelling slides and test tube
4. Tumor box®
5. Sterile compresses, scalpel, tweezers, and special liquid nitrogen-handling gloves and deuwer

Security directions for working with liquid nitrogen must be adhered to.

B. Procedure

At least two tumor pieces (A and B) should be taken from morphologically different areas. A and B tumor samples are to be divided into four equal-size portions.

Resectable tumors:

1. Dividing tumor specimens
   Performed jointly with the responsible pathologist: pathologist slices off tumor specimen and distributes for processing. Tissue specimens from at least two different representative areas should be obtained. Tissue from areas A and B and if possible, additional specimens from areas C, D etc. but not from tumor resection edges, connective tissue, necrotic areas, and tumor nodular components as these are archived in addition to tumor tissue specimens. If more specimens (C, D) are obtained, use new set of collection tubes. Divide specimens into 4 equal-size portions each: A1, A2, A3, A4 and B1, B2, B3, B4 (C1, C2, C3, C4 etc.). Carefully and steriley dab away blood from tumor tissue before processing. Process as quickly as possible (ideally within 30 minutes after surgical removal). Remaining tumor tissue is to be deposited into formalin solution for histological diagnostics (local pathologist).
   If pathologist does not need all remaining tumor tissue from large surgical preparations for diagnostics, slice remaining tumor tissue into small slices, freeze and ship in 50 ml collection tubes. The pathologist decides which addition tumor tissue can be frozen!

2. Shock-freeze fresh tissue
   Fill 50 ml collection tubes with liquid nitrogen and loosely cover so that slight evaporation can occur yet no pressure builds up.
   Label 1.8 ml standing collection tubes (red) with name, date of birth, surgery date and tumor localization (A2, etc.).
   Unscrew stoppers. Put deuwer lid on sterile compress and put precooled tubes in deuwer with liquid nitrogen.
   Sterilely unpack compresses, tweezers and scalpel and lay out.
   Wear sterile gloves (to protect tissue from RNase contamination from hands and to maintain general sterility).
   Divide tumor specimens A, B into 4 portions each: A1, A2, A3, A4, B1, B2, B3 and B4 (see sketch above); put portions A2, A3, A4, B2, B3; and B4 into collection tubes and sterile shock freeze. If portions do not fit into collection tubes, cut into smaller pieces.
   Shock freeze tissue by dropping into 50 ml vial of liquid nitrogen. Do not submerge with tweezers because tumor tissue will stick to tweezers. Also make sure that tissue portion does not stick to sides of 50 ml vial.
Decant liquid nitrogen from precooled 1.8 ml tubes. This means that no liquid nitrogen is to remain in the 1.8 ml tubes.

Transfer shock-frozen tumor tissue from 50 ml vial into red 1.8 ml tubes (keeping A and B portions separated), seal (screw caps), and keep frozen in liquid nitrogen.

Note time from tumor tissue removal to time frozen on shipping form.

3. Lab production of swab preparations and formalin tissue fixations

Label 2 containers for histology with name, date of birth and surgery date and fill with buffered 4% formalin solution (these containers are not included in the tumor specimen kit).

Produce 10 each tumor cell swab preparations from specimens A1 and B1. Gently dab surface cell layer of tumor specimen onto Superfrost slide (ca. 6 dabs per slide, max. 10 slides per tumor specimen, do not wipe).

Label preparations and air dry.

Deposit UNALTED tumor specimen portions A1 and B1 into separate containers of 4% formalin solution for histological assay of tumor cell characteristics by local pathologist.

Non-resectable tumors

1. Dividing tumor specimens

Tumor tissue distribution depends on size of biopsy and should be performed by the pathologist. If possible, the surgeon should remove specimens from 2 different tumor A and B areas (each ca. 1 cm³). Carefully and sterilely dab away blood from tumor tissue before processing. Depending on the biopsy size, a portion should be removed for histological diagnostics and remaining tumor tissue deep frozen in liquid nitrogen (see above). In smaller biopsies, the pathologist decides what should transpire and how much tissue can be frozen.

2. and 3. Same as Steps 2 and 3 for resectable tumors.

C. Obtaining comparative DNA and leucocytes isolation from citrated blood and/or normal tissue

Blood

Obtain 5–10 ml accompanying blood sample from patient in a Vacutainer® Monovette tube containing citrate (green), mix thoroughly (do not shake) and, wholly contained in thermo container, freeze with liquid nitrogen.

Tumor types: all

Fill glass Monovette tube (blue black stopper) with 4 ml blood. Do NOT deep freeze glass Monovette – send unfrozen in tumor box lid together with swabbed cell preparations.

Tumor types: all

Normal tissue

If for technical surgical reasons normal tissue is removed during the same operation, this tissue is even more advantageous for comparison purposes. However, under no circumstances should this lead to an additional resection or expansion of resection.

Tumor types: all

The comparison tissue is put in a green collection tube and frozen in liquid nitrogen.

D. Shipping

1. Fill out shipping form completely and send with the material in the tumor box to the responsible laboratory.

2. Ship tumor specimen portions A1, B1 (and C1, D1 etc. if available) in 4% formalin solution plus any remaining tumor tissue from responsible pathologist along with request for reference histology.

3. Ship shock-frozen tumor specimen portions A2, A3, A4, B2, B3, B4 (and C2, C3, C4 etc. if available) plus comparison blood sample and/or normal tissue stored at –70 to –80°C or in liquid nitrogen. Use express delivery and ship deep-frozen or on dry ice in tumor box to responsible molecular genetic laboratory. The entire tumor box must be totally filled with dry ice. The air-dried tumor swab preparations, glass Monovette and, if applicable, serum and bone marrow should be shipped enclosed in tumor box lid (not on dry ice).

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Tel: +49 (0)228-287 4398
Standardized rehabilitation measures

An investigation of the post-treatment long-term consequences and QoL in children and adolescents is one of the primary aims of KRANIOPHARYNGEOM 2007. Based on established somatic and intellectual/cognitive long-term problems, the goal is to define the support measures necessary to successfully rehabilitate craniopharyngioma patients. Optimizing rehabilitation includes early detection of patients requiring intensified rehabilitation efforts (e.g. hospital-provided obesity rehabilitation measures).

Scientific investigations of efficient hospital-provided rehabilitation measures in the follow-up care of obese craniopharyngioma patients do not yet exist. In collaboration with the Children's Hospital Hochried in Murnau, Germany, a standardized concept was worked out and successfully introduced over 5 years ago. Initial analyses of the therapy successes thus far indicate a high success rate and acceptance.

Patient information regarding rehabilitation provisions of craniopharyngioma patients

The rehabilitation of craniopharyngioma children and adolescents frequently poses huge challenges due to concentration and memory problems, sight impairment, school difficulties and problems at work, eating disorders and severe weight increase, as well as hormone deficiencies that require long-term medication. Specialized hospitals offering rehabilitation provisions pursue the goal of providing solutions to these challenges for patients and their families. Unfortunately the success of such measures is frequently only temporary.

Together with the Children's Hospital Hochried we developed rehabilitation measures specifically for children and adolescents having experienced craniopharyngioma. We hope that these rehabilitation provisions succeed because this disease presents very special problems for craniopharyngioma patients and their families:

- The small groups consist exclusively of patients of comparable age with the same disease (craniopharyngioma). Experience exchanges between concerned patients and their families are encouraged.
- Including mothers and fathers makes it possible to involve the family and parents in the patient’s rehabilitation.
- A hospital school enables ongoing school attendance for all school forms during rehabilitation so that no scholastic absentee time is accrued. A detailed investigation of school and learning problems should lead to individually-oriented help.
- After a medical examination, a program is arranged with every patient and/or parents on how lasting weight reduction and/or stabilization can be maintained – especially after attending the rehabilitation program.
- The time spent at the clinic and therapy during rehabilitation is designed so that rehabilitation can be repeated at regular intervals and can be based on the patient’s present experiences and previous stays.
- Only actual experience in dealing with problems of craniopharyngioma patients promises rehabilitation success. Rehabilitation quality should be secured by skilled personnel and scientific analysis of the successes and failings of the rehabilitation program.
- Close collaboration between Rehabilitation Hospital and the respective hospital/care physicians at the patient’s place of residence is necessary in order to improve the organization, execution and follow-up care associated with the rehabilitation program.
13. Checklists

13.1. Checklists: Preoperative diagnostics

**Anthropometric data (p. 52)**
- weight
- height
- Tanner pubertal stage (PH I-IV, B I-IV)

**Ophthalmological results (p. 54)**
- visual acuity
- optic nerve and optic disk examination (diopter range)
- field of vision

**Imaging (p. 53)**
- MRI before and after contrast agent
- CT without contrast agent (obligatory!)

**Lab tests (p. 55)**
- diabetes insipidus diagnostics (fluid intake/urine ratio, osmolality of 1st morning urine
- serum prolactin
- $\alpha_1$-fetoprotein and $\beta$-hCG in serum
- thyroid parameters (FT4, TSH)
- serum/salivary cortisol profile or free cortisol in 24h urine collection

**Documentation forms (pp. 153–159, 163)**
- Application form (pp. 153–154, send to German Pediatric Cancer Registry)
- Assessment Forms 0–4, Form 8 (pp. 155–159, 163)

**Functional capacity (pp. 58, 129)**
- Fertigkeitsenskala Münster-Heidelberg (FMH) – German-dev. ability scale

**Neuropsychological results (pp. 58–60) (if possible!)**
- Bayley Scale of Infant and Toddler Development III (BSID III)
- Coloured Progresses Matrices (CPM/SPM)
- Kaufmann Assessment Battery for Children (K-ABC)
- Hamburg-Wechsler Intelligence Test for Children IV; -Adults (HAWIK IV/HAWIWA/WIE)
- Developmental Test of Visual-Motor Integration (VMI)
- Continuous Performance Test (CPT)
- Child Behavior Checklist (CBCL)

**Quality of life measurements (s. page 61): (if possible!)**
- PEDQOL 8–18 y (patient and parent version)
- PEDQOL 4–7 y (patient and parent version)
- SDQ (patient and parent version)
- HIT-Leben (parent version)

Intraoperative removal and assay of CSF, cyst fluid, tissue for tumor banking (shipping instructions and address p. 115)
13.2. Checklists: Postoperative diagnostics

**Program for monitoring examinations 3 months post OP**

- MRI course monitoring + CT when appropriate
- Baseline QoL examination: PEDQOL 3rd month (60–90 days)
- Return completed PEDQOL questionnaire to Study Headquarters, Oldenburg
- Neuropsychological assessments (see instruments, pp. 58–60)
- Deadline (!) for patient application – randomization! (after incomplete resection, ≥5 y)

<table>
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<tr>
<th>History</th>
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<th>4–6 mths post OP</th>
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<td>CBCL</td>
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</table>

**QoL (p. 61)**

- PEDQOL 8–18 y | ○ | | ○ |
- PEDQOL 4–7 y | ○ | | ○ |
- SDQ | ○ | | ○ |
- CHQ | ○ | | ○ |
- Life situation | ○ | | ○ |

**Functional capacities (pp. 58, 129)**

- FMH | ○ | | ○ |

**Lab tests (p. 64)**

- Endocrine basal values (fT4, TSH, Cortisol, IGF-I) | ○ | | ○ |
- Stimulation testing (6 Mo post OP) | ○ | | ○ |

**Imaging diagnostics (p. 57)**

- Cranial MRI | ○ | | ○ |
- Cranial CT (as needed, i.e. calcifications) | ○ | | ○ |

**Documentation**

- Status assessment (form 6, p. 161) | ○ |
- Course documentation (form 5, p. 160) | ○ |

**In case of performed therapies:**
- Radiation Therapy Technique (form 3, p. 158)
- Radiology Reference Assessment (form 7, p. 162)
- Radiological monitoring of residual tumor every 3 months
14. Test protocols

Releasing hormone tests to check hypothalamic-pituitary axis
(GnRH-, TRH-, CRH- and GHRH-Test)
(Sippel 2005)

Frequent mistakes: Dry test substances are not dissolved completely or not completely transported into the syringes. After injection into a venous access, a portion of injected volume remains in the injection needle or is rinsed away with back running blood. Sufficient rinsing and carefully avoiding loss of injection volume are important.

GnRH test: GnRH is synthesized in hypothalamus and after diffusing into the surrounding capillary blood, causes pituitary to release gonadotropins FSH and LH. Lack of elevation of gonadotropins suggests an injured pituitary. The magnitude of serum gonadotropine elevation also sheds light on pubertal maturation level regulated by the hypothalamic-pituitary-gonadal axis. No GnRH test is necessary in prepubertal patients as no gonadotropin elevation is expected from LHRH administration in these patients. Side-effects: rare hypersensitive reactions.

TRH Test: Test principle: The hypothalamic releasing hormone TRH leads to secretion of TSH (thyrotropin stimulating hormone) from the anterior lobe of the pituitary gland. An impairment of TRH-stimulated TSH increases indicates an insufficiency in this function. There are no contraindications and no pre-test requirements. Complaints of short-term nausea and feeling flush are not unusual. Convulsions can be triggered by TRH in children with epileptic disorders or in those with an inclination for convulsions. TRH and/or GnRH have also been reported to cause acute pituitary infarction (pituitary apoplexy) (Masago 1995; Masson 1993). Intranasal and oral TRH tests are unreliable in children.

CRH Test: Corticotropin-releasing hormone (CRH) is produced by the hypothalamus and is transported to the anterior lobe of the pituitary, where it stimulates corticotrope cells to secrete corticotropin (ACTH), which in turn stimulates cortisol secretion from the adrenal cortex. There are no contraindications. Side-effects: flushing sensation, brief metallic taste, and an occasional slight drop in blood pressure. Do not perform saliva profiling (morning, noon and evening saliva samples) the day of the CRH test. Basal values > 200 nmol/l (7.2 µg/dl) and a 50% climb in cortisol should cause no alarm (Quabbe 1993).

GHRH Test: Hypothalamic releasing hormone GHRH administration leads to binding to specific receptors that release GH from the anterior lobe of the pituitary. Pre-test requirements: fasting for a minimum of two hours before test; test can be performed any time during the day. There are no contraindications. Side-effects: ca. 14% of the patients experience short-term flushing, paleness, peculiar taste in the mouth, headache and nausea are possible in ca. 1% of patients (Chatelain 1987).

The GHRH test has limited clinical relevance. The GHRH test result is subject to large intra- and interindividual variability (Chatelain 1987; Ghigo 1996) and the test can also fail to show a significant GH elevation in even healthy subjects (e.g. through high somatostatin tone or postprandial somatostatin). Obesity can negatively influence the test. The GHRH test is not suited for testing GH deficiency because the results do not correlate with the classic GH stimulation tests (arginine infusion test, IHT insulin hypoglycemia test).
Releasing hormone tests to check hypothalamic-pituitary axis

Patient: Date of birth: Date of Test:
Height: Weight: Body surface (BSA):
Examiner: Nurse:

1. Baseline blood sample drawn before test begins (serum labelled as 0-value)
Intravenous administration of test substances (bolus injections) at__________ hour

   60 ug LHRH / m² BSA = __________ug LHRH i.v.
   100 ug TRH / m² BSA = __________ug TRH i.v. (max. 200 ug)
   1 ug GHRH / kg body wt. = __________ug GHRH i.v.
   1 ug CRF / kg body wt. = __________ug CRF i.v.

2. Blood sample: 30 min. after injection of test substances at__________ hour
(serum)

3. Blood sample: 60 min. after injection of test substances at__________ hour
(serum)

Determination of GH, TSH, cortisol, prolactin, LH and FSH
in baseline serum samples and in samples drawn at 30 min. and 60 min.
Test principle: Clonidine is a central alpha-adrenergic agonist. The increase in growth hormone (GH) levels after clonidine stimulation is not mediated through GHRH. Next to the GHRH arginine stimulation test, clonidine is the strongest pharmacological GH stimulus in clinical use.

Contraindications: none.

Preparation and execution: Prepare a venous access one hour before test begins. Draw 1st blood sample to determine basal GH level (0-minute). Then orally administered clonidine in a dosage of 0.075 mg per m² body surface area (BSA). Draw subsequent blood samples for blood sugar determination at 30, 60, 90 and 120 minutes following single administration of clonidine. Parallel GH levels result.

Test symptoms: Tiredness and sleepiness. Hypoglycemia is expected to be found in 2–3% of patients during protocol course monitoring. Observation of patient is necessary during and after the test.

Test assessment: A GH increase of > 15 ng/ml after 60–90 min. counts as a normal result.

Clinical remarks: The appropriate clonidine dose of 75 ug per m² BSA usually does not cause a drop in blood pressure – which is only expected after administration of 0.15 mg clonidine per m² BSA. Intra-individual reproducibility of the clonidine test is somewhat better than that of the arginine test but incorrect low GH level increases are a downside of clonidine testing. The literature emphasizes this point, making arginine testing the best choice when measuring sensitivity and specificity of growth hormone deficits.

**Clonidine Test:**

<table>
<thead>
<tr>
<th>Date of Test:</th>
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</table>

<table>
<thead>
<tr>
<th>Weight:</th>
<th>Height:</th>
<th>Body surface (BSA): ____ m² BSA</th>
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<tbody>
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<table>
<thead>
<tr>
<th>Examiner:</th>
<th>Nurse:</th>
<th>Patient/Parents briefed?</th>
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<tbody>
<tr>
<td>___________</td>
<td>___________</td>
<td>____ yes ____ no</td>
</tr>
</tbody>
</table>

**Process:** at each blood sample draw: 1.5 ml blood + assay of blood sugar (BS) bedside

75 ug oral clonidine per m² BSA = ____ug oral clonidine

1st sample: 1.5 ml 60 min. before oral clonidine admin. BS _____ mg/dl, time: ____hour

2nd sample: 1.5 ml 30 min. after oral clonidine admin. BS _____ mg/dl, time: ____hour

3rd sample: 1.5 ml 60 min. after oral clonidine admin. BS _____ mg/dl, time: ____hour

4th sample: 1.5 ml 90 min. after oral clonidine admin. BS _____ mg/dl, time: ____hour

5th sample: 1.5 ml 120 min. after oral clonidine admin. BS _____ mg/dl, time: ____hour

*Protocol for clinical symptoms and test course:

Test course protocol dictates registering pulse, blood pressure, consciousness and hypoglycemic symptoms such as hunger, paleness, sweating, vertigo, etc. Further measurements of blood sugar levels may be necessary and must be measured immediately after drawing blood. The release of the patient is only possible if the patient is completely awake, free of complaints, and has consumed an adequate meal.
Desmopressin / DDAVP Test
(Sippell, 2005)

**Test principle:** Healthy people concentrate urine ca. 900–1200 mosmol/kg after about 12–16 hours of fluid deprivation whereas patients with central diabetes insipidus can concentrate their urine usually only < 250 mosmol/kg. A thirst experiment to verify diabetes insipidus is not recommended due to the danger of a fluid deficit and hypotensive circulation disturbances. The recommended alternative is to determine osmolality in the first morning urine and obtain a serum sample at the same time, making a simultaneous exact determination of fluid intake and urine output ratio. The desmopressin test is recommended in cases of polyuria / polydypsia and diabetes insipidus as both a diagnostic and initial therapeutic measure.

**Procedure:** Measure fluid intake and urine export as well as osmolality in serum and urine before and after i.v. administration of desmopressin (dose: 0.5 µg/m² for infants; 2 µg/m² for children).

---

Arginine Infusion Test
(Sippell, 2005)

**Test principle:** The amino acid arginine stimulates growth hormone secretion through alpha-adrenergic and serotonin stimuli as well as through somatostatin suppression.

**Contraindication:** acidosis, restricted liver or kidney function.

**Pre-testing requirements:** Patient restricts food intake (water permitted) the morning of test execution. It is recommended to do venous access the evening before when testing children to avoid stress-contingent falsified test results.

**Side-effects:** late hypoglycemia is possible, especially in children with dystrophia and in undernourished adults (arginine is also a secretagogue for insulin). Test can exacerbate a pre-existing acidosis condition (blood gas analysis monitored) and can cause vomiting in rare cases.

**Evaluation:** GH maximum >10 ng/ml in 30–60 min. excludes a classic but not a functional hypothalamic growth hormone deficiency (neurosecretory dysfunction). A combination of an arginine infusion test with a GHRH test and/or TRH test is possible. The arginine infusion test has a relatively low sensitivity and specificity (Youlton 1969; Hindmarsh 1995). It is to be calculated with a possible incorrectly low result of up to 25% (Tassoni 1990). The correlation between the GH maxima in a test repetition is low (Youlton 1969; Zadik 1990). Correspondingly, a high intraindividual variation coefficient (4–125%) has been found for the GH maxima (Hindmarsh 1995; Tassoni 1990).
Arginine Infusion Test:  

Body weight:  

Examiner:  

**Procedure:**  

1. **Blood sample:** 30 minutes before infusion starts: 1.5 ml blood in serum tube  

2. **Blood sample** (1.5 ml blood in serum tube): at infusion start  

0.5 g L-arginine hydrochloride/kg body wt. 
short (30 min.) i.v. infusion (max. 30 g)  

\[ \text{Calculated quantity (ml) arginine hydrochloride 21.07% in equal volume NaCl 0.9% Sol.} \]  

Infusion start: \( \text{hour} \)  
Infusion end: \( \text{hour} \)  

3. **Blood sample** 30 min. after infusion start: 1.5 ml blood \( \text{hour} \)  

4. **Blood sample** 60 min. after infusion start: 1.5 ml blood \( \text{hour} \)  

5. **Blood sample** 90 min. after infusion start: 1.5 ml blood \( \text{hour} \)  

6. **Blood sample** 120 min. after infusion start: 1.5 ml blood \( \text{hour} \)  

Immediately discontinue arginine infusion upon allergic reaction!  

---  

Peculiarities/observable features during test execution:
**Oral Glucose Tolerance Test**
(Sippell, 1999)

**Test principle:** Oral glucose load (children: 1.75 g/kg body wt.) increases blood sugar level. Exceeding the defined limit indicates disturbed glucose tolerance or a diabetic metabolism.

**Contraindication:** development of diabetes mellitus

**Pre-testing requirements:** No food (fluids permitted) for 10–16 hours. No fluids except water from evening before until morning of test.

**Common mistakes:** Ignoring deviation from capillary/venous blood or plasma standard values. Testing using self-measuring blood sugar devices instead of using required wet chemical method. Incorrect calculation of glucose load (glucose load corresponds to anhydrous glucose).

**Oral Glucose Tolerance Test:**

Weight:  
Examiner:

**Procedure:**

1. **Fasting glucose measurement (0 minute)**

2. Children drink 1.75 gram glucose / kg body wt. in 300 ml water  
   Adolescents and adults drink 75 gram glucose in 300 ml water

3. after 60 minutes: blood sample for glucose measurement
4. after 120 minutes: blood sample for glucose measurement
5. no physical activity during test

**Peculiarities/observable features during test execution:**

**Evaluation:** according to WHO criteria (WHO Study Group, 1985)

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<th>Blood (capillary)</th>
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<td>&lt;7.8 mmol/l</td>
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Relapse Pattern After Complete Resection and Early Progression After Incomplete Resection of Childhood Craniopharyngioma

Abstract

In the HIT-Endo data on therapy and prognosis of 306 patients with childhood craniopharyngioma (CP) were analyzed. The 5-year overall survival rate was 94 ± 4% in irradiated patients and 93 ± 5% in non-irradiated patients. Aims of the prospective study KRANIOPHARYNGEOM 2000 were to collect data on the incidence and time course of relapses after complete surgery and tumour progressions after incomplete resection. Furthermore, the impact of irradiation therapy (XRT) on tumour relapse and recurrence rates was analyzed. Since 2001 ninety-eight patients with CP were recruited at a median age at diagnosis of 9.9 years ranging from 1.8 to 18.0 years. Complete resection was achieved in 44%, incomplete resection in 54%. XRT was performed in 24 of 58 CP patients; in 10 early after incomplete resection, in 4 of 24 after progression of residual tumour or relapse, in 3 of 14 after second surgery of relapse. XRT was performed at a median age of 12.0 years ranging from 5.0 to 18.9 years and in median after an interval of 9 months after first diagnosis. The analysis of event-free survival rates (EFS) in patients with CP showed a high rate of early events in terms of tumour progression after incomplete resection (3y-EFS: 0.22 ± 0.09) and relapses after complete resection (3y-EFS: 0.00 ± 0.10) during the first three years of follow-up. A high rate of early events (1y-EFS: 0.76 ± 0.10; 2y-EFS: 0.57 ± 0.15) was also found for patients after XRT (3 cystic pro-

Zusammenfassung

In der Querschnittsstudie HIT-Endo wurden 306 Kinder und Jugendliche mit Craniopharyngiom (CP) hinsichtlich Therapie und Langzeitprognose untersucht. Die 5-Jahre-Gesamtüberlebensraten lagen bei 94 ± 4% für bestrahlte Patienten und bei 93 ± 5% für nicht bestrahlte Patienten. Die prospektive Beobachtungstudie KRANIOPHARYNGEOM 2000 untersucht die Rezidivrate nach kompletter Resektion und die Progressionsraten nach inkompletter Resektion des CP sowie den Einfluss der Strahlentherapie (XRT) auf Häufigkeit und zeitliches Auftreten von Rezidiven und Tumorprogressionen. Seit 2001 wurden 58 CP-Patienten rekrutiert und prospektiv untersucht. Das mediane Alter bei Diagnose lag bei 9.9 Jahren (1–18). 24 CP-Patienten wurden bestrahlt in einem medianen Alter von 12 Jahren (5–15), im Mittel 9 Monate nach Diagnose. Eine Zwischenanalyse zur ereignisfreien Überlebenszeit (EFS nach 3 Jahren) ergab hohe Raten an frühen Ereignissen im Sinne von Tumorprogressionen nach inkompletter Resektion (3y-EFS: 0.22 ± 0.09) bzw. Rezidiven nach kompletter Resektion (3y-EFS: 0.60 ± 0.10). Auch nach XRT fanden sich frühe Ereignisse (1y-EFS: 0.76 ± 0.10; 2y-EFS: 0.57 ± 0.15) 3 Zystenprogressionen und 3 progrediente solide CP-Anteile nach XRT. Wir schlussfolgern, dass Rezidiv nach kompletter Resektion bzw. Tumorprogression nach inkompleter Resektion des CP auch nach XRT häufige Ereignisse im Fäl-
gressions, 3 progressions of solid tumour; in 24 patients after XRT). We conclude that tumour progression and relapse are frequent and early events even in irradiated patients. Monitoring of cerebral imaging and clinical status is recommended in follow-up of patients with childhood CP. In order to analyze the appropriate time point of XRT after incomplete resection, QoL, EPS and overall survival in patients (age ≥ 5 years) will be analyzed in KRAINOPHARYNGEOM 2007 after stratified randomization of the time point of irradiation after incomplete resection (early irradiation versus irradiation at progression of residual tumour).

Key words
Childhood craniopharyngioma - survival - irradiation - hypothalamus

Introduction
Craniopharyngiomas are tumorous embryonic malformations which arise from ectodermal remnants of Rathke's pouch. Thus craniopharyngioma can be found anywhere along the path of development of Rathke's pouch in hypothalamic and pituitary regions, which are of importance in endocrine regulation [2–3]. Craniopharyngiomas are the most common intracranial tumors of non-glial origin in the pediatric population, constituting between 6 to 9% of pediatric brain tumors. Overall there are 0.5 to 2 new cases per million population occurring each year, 30 to 50% of which are children and adolescents [16]. The peak incidence is at age 5 to 10 years but they can occur at any age, including infancy and pre- and neonatal periods. Although the tumour itself is of low grade histological malignancy and the overall survival rate of patients is high (92%), there is considerable morbidity even if the tumour can be resected completely [4, 7, 11 – 17]. In spite of sufficient substitution of hormonal deficits, obesity is present postoperatively in up to 52% of patients with at least one half of these patients having severe difficulty controlling their desire to eat [8 – 10, 20].

Prospective multicenter studies analyzing the impact of various therapeutic strategies on prognosis in patients with childhood craniopharyngioma do not yet exist. Therefore the dispute among advocates supporting a radical surgical treatment and those favoring a biopsy followed by radiation therapy is not settled yet. Accordingly, KRAINOPHARYNGEOM 2000 a prospective, multicenter surveillance study was initiated [18]. The major aim of the study is to evaluate diagnostic and therapeutic modalities with regard to effectiveness and implication on quality of life.

We report on an interim survival analysis of patients recruited in HIT Endo and KRAINOPHARYNGEOM 2000 and the design of the new prospective study KRAINOPHARYNGEOM 2007.

Subjects and methods

Schlüsselwörter
Krainopharyngioma · Gesamttüberleben · Strahlentherapie · hypothalamus

(n = 306) and in a multicenter prospective surveillance study (KRAINOPHARYNGEOM 2000) on children and adolescents with craniopharyngioma (n = 98) [18] initiated in 2001. Informed consent was obtained from parents and both studies were approved by the local standing committee on ethical practice.

In 306 patients recruited in HIT Endo childhood craniopharyngioma was diagnosed at a median age of 8.3 years (ranging from 2 weeks to 20.5 years). Focal irradiation was performed in 70 patients (43%) with a cumulative dose of 54 Gray (Gy) and single daily doses of 1.8 Gy. The median follow-up period was 8.0 years, ranging from 0.07 to 36.5 years. The median age at latest follow- up was 17.6 years (range: 1.5 – 44.5 years). Health related quality of life (QoL) could be analyzed in 22 irradiated patients and in 16 non-irradiated patients recruited in HIT Endo using the PEDQOL questionnaire [8].

98 patients were recruited in KRAINOPHARYNGEOM 2000 [10] 01–03/06 and analyzed based on prospective evaluation. Childhood craniopharyngioma was diagnosed at a median age of 9.4 years ranging from 1 to 17 years. Tumour diagnosis was confirmed by histology in all cases. Hypothalamic involvement and the degree of surgical resection was assessed by reference evaluation of all imaging [23]. 49 patients (50%) presented with a craniopharyngioma involving hypothalamic structures. Focal irradiation was performed in 24 patients (24%) with a cumulative dose of 54 Gray (Gy) and single daily doses of 1.8 Gy.

Results are expressed as medians and ranges, unless otherwise indicated. Statistical differences between patient groups described below are estimated by Fisher's exact test for a binary variable, by t-test for a normally distributed variable and by log-rank test for survival time or event free survival time. Statistical analysis was performed using commercial software programs and supervised by the Institute for Medical Biostatistics, Epidemiology and Informatics, University of Mainz, Germany.

Results
The 5-years-overall survival rate in 360 patients recruited in HIT Endo was 94 ± 4% in irradiated patients and 93 ± 5% in non-irra- diated patients. Differences between irradiated (n = 22) and non-

irradiated (n = 16) patients in terms of quality of life (PedsQL questionnaire) did not reach statistical significance during long-term follow-up (data not shown).

Between October 2001 and March 2006 ninety-eight patients with childhood craniopharyngioma were reported to the German childhood cancer registry from 30 centers (54% oncological, 32% endocrine, 10% paediatric departments, 7% others). With a high degree of completeness (80-90%) data on neurosurgery, pathology, initial diagnostic imaging, irradiation, endocrine deficiencies and substitution and QoL could be collected prospectively during follow-up. Complete resection was achieved in 54% (n = 44), incomplete resection in 44% of all cases (n = 23). MRI was performed in 50 of 90 patients (6 patients unknown); in 10 of 24 early after incomplete resection, in 14 of 24 after progression of residual tumour or relapse. In 5 of these 14 patients XRT was performed after second surgery of relapse. Data on XRT modalities were evaluable in 17 of 24 patients. XRT was performed at a median age of 12 years ranging from 5.0 to 18.9 years and in median after an interval of 9 months after first diagnosis. All patients got a 3-dimensional CT-planning of XRT. The mean total dose was 52.5 Gray (Gy) ranging from 50.4 to 60 Gy.

Fig. 1 Kaplan-Meier curves of event-free survival (EFS) in all patients (a) and in non-irradiated patients recruited in KRANIOPHARYNGEOM 2000 [18] in relation to the degree of resection (b), no hypothalamic involvement (c), and the degree of obesity (d).
We performed an interim evaluation on event-free survival rates (EFS) after four years of patients' recruitment in KRANIOPHARYNGEOM 2000 analyzing 3 years-EFS in relation to treatment strategies, risk factors for impaired QoL and late effects. The analysis showed a 3y-EFS of 0.40 ± 0.07 for the total group of evaluable patients (n = 88) [Fig. 1a] and a high rate of early events in terms of tumor progression after incomplete resection (3y-EFS: 0.22 ± 0.08; n = 48) and relapses after complete resection (3y-EFS: 0.60 ± 0.10; n = 37) during the first three years of follow-up (p = 0.007). The degree of neurosurgical resection had similar negative impact on EFS rates in the cohort of non-irradiated patients (complete resection: n = 32, 3y-EFS 0.67 ± 0.10; incomplete resection: n = 27, 0.23 ± 0.13; p = 0.013) [Fig. 1b].

In the total group of patients EFS was not related to hypothalamic tumor involvement (hypothalamic involvement: n = 40, 3y-EFS 0.35 ± 0.10; no hypothalamic involvement: n = 28, EFS 0.56 ± 0.10) [Fig. 1c] and the degree of obesity (BMI < 2 SD: n = 39, 3y-EFS: 0.50 ± 0.11; BMI ≥ 7 SD: n = 36, 3y-EFS: 0.35 ± 0.09; BMI > 7 SD: n = 11, 3y-EFS 0.42 ± 0.16) [Fig. 1d]. Furthermore, a high rate of early events (tumor progression: 2y-EFS: 0.57 ± 0.15) was also found for patients after XRT (3 recurrences, 3 recurrences of solid tumor, in 24 patients after XRT) [Fig. 2].

Discussion

The survival analysis of patients prospectively recruited in the German multicenter study KRANIOPHARYNGEOM 2000 showed high rates of early events in terms of tumor progression after incomplete resection (3y-EFS 0.22 ± 0.08) and relapses after complete resection (3y-EFS 0.60 ± 0.10) during the first three years of follow-up. At 3 years prospective follow-up the EFS rates after complete and incomplete resection are lower when compared with reports from the literature [1–3]. A possible explanation for this discrepancy could be the fact that most reports in the literature are based on single-center retrospective analysis of small patient cohorts. Such single-center evaluations tend to observe better results when compared with multicenter prospective studies.

Recent reports show that tumor size, number of neurosurgical interventions, involvement of hypothalamic structures, the visual system or skull base structures have significant impact on.
operability and long-term prognosis [11] besides the surgeon’s expertise. Based on our observation of frequent and early tumour progressions after incomplete resection innovative treatment strategies should be discussed for these patients. As radical surgery is not appropriate in case of hypothalamic involvement, patients with residual tumour represent the group at risk for impaired long-term prognosis. Therapeutic alternatives such as intracavitary (P32, Bleomycin) or interstitial modalities (stereotactic) as well as gammaknife XRT should be taken into therapeutic consideration, especially in infants with mainly cystic components of craniopharyngioma.

The appropriate time point of irradiation after incomplete resection is controversial in the literature as well as in the clinical settings. Immediate postoperative irradiation is favored due to the speculation that tumour progression associated with life-threatening complications could be prevented. Supporters of irradiation at progression of residual tumour argue that such risk adapted strategy is effective and prevents unnecessary radiogenic sequelae. Stripp et al. [21] could demonstrate that immediate postoperative irradiation resulted in a longer interval to tumour progression. The overall survival was not influenced by the time point of irradiation in this study. The authors conclude that irradiation given either early after incomplete resection or at progression is effective in controlling craniopharyngioma. In our study we found early tumour progression also in patients after irradiation. However, the final study evaluation two years after end of recruitment will answer the question whether this observation reflects a short-term delay of radiogenic tumour effect. Efficacy, feasibility and prognostic impact of intracavitary and interstitial treatment options will be analyzed as well two years after end of recruitment.

Tomita et al. [22] reported on relapse-free survival rates of 83% and 70% at 5 and 10 years after complete resection, respectively. The progression-free survival rates after incomplete resection followed by irradiation were 71% and 36% after 5 and 10 years, respectively. The progression-free survival rate after complete resection was significantly lower in non-irradiated patients (Sy-EFS: 9%). Irradiation at the time of progression of residual tumour after incomplete resection was effective and resulted in overall survival and progression-free survival rates of 90% and 70%, respectively.

Moon et al. [5] analyzed 50 patients with childhood craniopharyngioma in a single center retrospective study and found no difference in terms of progression-free survival and quality of life (Qol) between the group of patients who received early irradiation after incomplete resection and the group of patients who were irradiated at the time of tumour progression after incomplete resection. However, Qol was estimated based on ophthalmological evaluation and salt-water imbalances. Instruments for self-assessment of Qol were not used in this study.

Based on the results of our interim analysis of KRANIOPHARYNGEOM 2000 we conclude that radical surgery is no appropriate treatment strategy in patients with hypothalamic involvement of childhood craniopharyngioma. In patients with mainly cystic tumour components intracavitary and interstitial treatment options should be considered. For patients after incomplete resection innovative treatment strategies are warranted due to high progression rates of residual tumour. In HIT Endo Qol was similar in irradiated and non-irradiated patients. Accordingly, in KRANIOPHARYNGEOM 2007 Qol, EFS and overall survival in patients (age > 5 years at diagnosis: incomplete resection) will be analyzed after stratification (according to postoperative Qol) randomization of the time point of irradiation after incomplete resection (early irradiation versus at progression of residual tumour) (Fig. 3). Regular monitoring and imaging is recommended also in patients after irradiation in order to detect and treat progressions at an early stage. All patients with complete resection and patients of an age > 5 years after incomplete resection will be recruited in the surveillance study KRANIOPHARYNGEOM 2007. The schedule of prospective data collection and the set and definition of parameters is based on a European consensus achieved in the craniopharyngioma subgroup of the SIOP brain tumour committee [6]. Standardized European data sets on a rare disease such as childhood craniopharyngioma will help to increase cohort sizes and facilitate common data evaluation [19].

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References

Zertifizierungsschreiben der Deutschen Krebsgesellschaft (DKG) vom 15.12.2006

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Hämatologie/Onkologie
Klinik für Allgemeine Kinderheilkunde
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Frankfurt, den 15. Dezember 2006

Durch Wisser Zum Leben
Deutsche Krebgesellschaft e.V. · Steinlestraße 6 · 60596 Frankfurt

nachrichtlich: Frau Heymann

Sehr geehrter Herr Doktor Müller,


Dies setzt noch voraus, dass Sie die Studie im Deutschen Krebsstudienregister unter www.studien.de eintragen (ist Bestandteil des Gütesiegels A).


Wir bedanken uns bei Ihnen für die konstruktive Zusammenarbeit und wünschen Ihnen und den Studienteilnehmern viel Erfolg bei der Durchführung der Studie.

Mit freundlichen Grüßen

[Unterzeichnet]

Prof. Dr. K. Possinger
Kommissionsvorsitzender

[Unterzeichnet]

Inga Rossion
Koordination Studienhaus Onkologie

[Adresse und Telefoninformation]
## Craniopharyngioma - Prospective observational study

### DATA AT DIAGNOSIS

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### Symptoms before diagnosis

- **Growth decline:**
  - yes
  - no
  - duration: ______ months

- **Weight gain:**
  - yes
  - no
  - duration: ______ months

- **Polyuria / Polydypsia / DI:**
  - yes
  - no
  - duration: ______ months

- **Incidental finding:**
  - yes
  - no
  - duration: ______ months

- **Neurological findings:**
  - yes
  - no
  - duration: ______ months

- **Headaches:**
  - yes
  - no
  - duration: ______ months

- **Visual disorders:**
  - fields
  - optic atrophy
  - acuity
  - squint
  - yes
  - no
  - duration: ______ months

### Preoperative endocrine findings

- **Diabetes insipidus**
  - yes
  - no

- **Hypothyroidism**
  - yes
  - no

- **Growth hormone deficiency**
  - yes
  - no

- **Hypocortisolism**
  - yes
  - no

- **Hypogonadism**
  - yes
  - no

### Puberty:

- **Pubertas tarda**
  - yes
  - no

- **Pubertas praecox**
  - yes
  - no

### Behavioural abnormalities

- yes
- no

### Hypothalamic syndrome

- yes
- no

( food-seeking behaviour/morbid obesity, somnolence/sleep disturbance, temperature instability)

### Remarks:

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**Address/Fax to Data Centre within 3 months**

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## Craniopharyngioma - Prospective observational study

**NEUROSURGERY RECORDING FORM**

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**Country**

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- Initials □□

**date of first surgery:**

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**Surgeon:**

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<tr>
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**Surgical approach to tumour**

- Open/Transcranial □
- Transphenoidal □
- Endoscopic □

- Pituitary stalk (intraoperativ): cut □
- Hypothalamic infiltration (intraoperativ): yes □

### Second surgery intervention

**date of 2. surgery:**

**Planned OP Procedures**

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**Surgical approach to tumour**

- Open/Transcranial □
- Transphenoidal □
- Endoscopic □

- Pituitary stalk (intraoperativ): cut □
- Hypothalamic infiltration (intraoperativ): yes □

### Histology:

- yes □
- no □

### Peri-operative complications (within 30 days of surgery):

- subdural effusion □
- strokes □
- new visual disturbance □
- blood transfusion requirement □
- CSF infection □
- severe salt and flood balance review □

**Remarks:**

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<th>Length</th>
<th>Width</th>
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</table>

<table>
<thead>
<tr>
<th>Volume (90%-Isodose) (ccm):</th>
<th>ccm</th>
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<tbody>
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</table>

<table>
<thead>
<tr>
<th>Radiation technique:</th>
</tr>
</thead>
<tbody>
<tr>
<td>3D-Planning</td>
</tr>
<tr>
<td>Yes</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Seed-Implantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
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<table>
<thead>
<tr>
<th>Date:</th>
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</thead>
<tbody>
<tr>
<td>D D M M Y Y Y Y</td>
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<table>
<thead>
<tr>
<th>Emitter:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radium</td>
</tr>
<tr>
<td>Yttrium</td>
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</table>

<table>
<thead>
<tr>
<th>of radio-isotope:</th>
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<tbody>
<tr>
<td>Phosphorus</td>
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<table>
<thead>
<tr>
<th>Date</th>
<th></th>
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<tbody>
<tr>
<td>D D M M Y Y Y Y</td>
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</table>

<table>
<thead>
<tr>
<th>Complications during RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical intervention during RT</td>
</tr>
<tr>
<td>Interrupted or delayed treatment programme</td>
</tr>
<tr>
<td>Planning change during treatment</td>
</tr>
<tr>
<td>Acute or delayed radiation oedema/ toxicity</td>
</tr>
<tr>
<td>No complications</td>
</tr>
</tbody>
</table>

Address/Fax to Data Centre within 3 months

<table>
<thead>
<tr>
<th>Date</th>
<th>stamp</th>
<th>signature</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
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</tbody>
</table>
## Craniopharyngioma – Prospective observational study

**STATUS, RELAPSE AND DEATH**

<table>
<thead>
<tr>
<th>Date of Birth</th>
<th>Date of Diagnosis=Surgery</th>
<th>Centre ID</th>
<th>Patient ID</th>
<th>Male</th>
<th>Female</th>
<th>Initials</th>
</tr>
</thead>
<tbody>
<tr>
<td>D D M M Y Y</td>
<td>D D M M Y Y Y Y</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Hospital</th>
<th>City</th>
<th>Country</th>
</tr>
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<td></td>
<td></td>
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</tbody>
</table>

**Status at follow up**

**Examination Date:**

<table>
<thead>
<tr>
<th>D D M M Y Y</th>
</tr>
</thead>
</table>

**Status of patient**

- [ ] Alive - free from tumour
- [ ] Alive with post op residual tumour
- [ ] relapse after complete resection
- [ ] progression of residual tumour
- [x] Dead

**comments:**

| …………………………………………………………………………………….|  |
|---------------------------------------------------------------------|  |

**Relapse/ progression treatment**

<table>
<thead>
<tr>
<th>Date: D D M M Y Y Y</th>
</tr>
</thead>
</table>

- [ ] no treatment
- [ ] surgery
  - [ ] complete
  - [ ] subtotal
- [ ] radiotherapy
- [ ] cyst drainage
- [ ] ventriculo-peritoneal shunt
- [ ] instillation of radioisotopes
  - [ ] phosphorus
  - [ ] yttrium
  - [ ] radium
- [ ] instillation of e.g. Bleomycin
- [ ] other ___________________  

**Death**

<table>
<thead>
<tr>
<th>Date: D D M M Y Y Y</th>
</tr>
</thead>
</table>

**Cause:**

- [ ] primary tumour disease
- [ ] cannot differentiate if tumour or treatment
- [ ] relapse/ progression
- [ ] second malignancy
- [ ] treatment related mortality
- [ ] other cause………………………………………
- [ ] hypopituitarism
- [ ] cardiovascular cause (eg strokes)

**Remarks:**

| …………………………………………………………………………………….|  |
|---------------------------------------------------------------------|  |

**Address/Fax to Study Centre within 3 month**

**Date:**

| Name: | Signature: |
Craniopharyngioma - Prospective observational study

**Follow Up**

<table>
<thead>
<tr>
<th>Date of Birth</th>
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<th>Centre ID</th>
<th>Patient ID</th>
</tr>
</thead>
</table>

Male ☐ Female ☐ Initials ☐

Hospital.........................................                      City........................ …         Country..................................

**Anthropometric data**

Examination Date  ____________ ____________

Measured body height (cm) ____________ ____________

Measured body weight (kg) ____________ ____________

Pubertal (PH) stage (Tanner) ☐

Pubertal (B) stage (Tanner) ☐

**Symptoms in the course**

Growth decline: ☐ yes ☐ no

Weight gain: ☐ yes ☐ no

Polyuria / Polydypsia / DI: ☐ yes ☐ no

Neurological findings: ☐ yes ☐ no

Headaches: ☐ yes ☐ no

Visual disorders: ☐ yes ☐ no

- fields
- optic atrophy
- acuity
- squint

**Endocrine findings:**

Diabetes insipidus ☐

Hypothyroidism ☐

Growth Hormone deficiency ☐

Hypogonadism/Hypocortisolism ☐

Puberty:

- Pubertas praecox ☐
- Pubertas tarda ☐

**Behavioural abnormalities** ☐ yes ☐ no

**Hypothalamic syndrome** ☐ yes ☐ no

(food-seeking behaviour/morbid obesity, somnolence, sleep disturbance, temperature instability)

**Medication:**

- Growth hormone: ☐ yes ☐ no
- L-Thyroxine: ☐ yes ☐ no
- Minirin/DDAVP: ☐ yes ☐ no
- Glucocorticoids: ☐ yes ☐ no
- Sex steroids: ☐ yes ☐ no
- Psychopharmaceuticals: ☐ yes ☐ no
- Sleep modifying drugs ☐ yes ☐ no
- Others: ___________________________

**Remarks:**

Address/Fax to Data Centre within 3 months

Date stamp signature