Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPOH)
Deutsche Gesellschaft für Kinderendokrinologie und Diabetologie (DGKED),
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Arbeitsgemeinschaft Pädiatrische Radioonkologie (APRO),
der Deutschen Gesellschaft für Radioonkologie (DEGRO)

KRANIOPHARYNGEOM Registry 2019

Multicenter registry for patients with childhood-onset craniopharyngioma, xanthogranuloma, cysts of Rathke's pouch, meningioma, pituitary adenoma, arachnoid cysts

Registry Protocol

In collaboration with:
Gesellschaft für Neuropädiatrie (GNP)
Neurologische Arbeitsgemeinschaft (NOA) der Deutschen Krebsgesellschaft (DKG)
Deutsche Gesellschaft für Neuroradiologie (DGNR)
Deutsche Gesellschaft für Neurochirurgie (DGNC)
Deutsche Ophthalmologische Gesellschaft (DOG)
Gesellschaft für Neuropsychologie eV (GNP)
Arbeitsgemeinschaft Adipositas im Kindes- und Jugendalter (AGA) der Deutschen Adipositasgesellschaft (DAG)
International Society of Paediatric Oncology (SIOP)
Deutsches Kinderkrebsregister (DKKR)

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IMPORTANT POINTS

This current multicenter registy on children and adolescents with craniopharynogioma applies a multidiscipline approach encompassing diagnostics, therapies and follow-up care associated with neuropediatrics, pediatric oncology, neuroradiology, neurosurgery, radiation therapy, neuropsychology, neuroimaging and pediatric endocrinology.

KRANIOPHARYNGEOM Registry 2019 is open to collaborative studies in its pursuit of multicenter, interdisciplinary participation and cooperation. Material and data will be made available to KRANIOPHARYNGEOM Registry 2019 colleages with study commission approval.

KRANIOPHARYNGEOM Registry 2019 is a prospective, multicenter registry that assesses the prognosis of craniopharyngioma patients in the context of the various currently practiced therapy strategies. Furthermore, long-term prospective follow-up observation of previously recruited patients in HIT-ENDO and KRANIOPHARYNGEOM 2000/2007 is performed as described and anticipated in these previous trials. The KRANIOPHARYNGEOM Registry 2019 is also in line with the perpetuation of reference assessments in the context of the HIT network in order to safeguard the achieved high quality standards.

This registry protocol was compiled with the greatest of 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 registry coordinator accepts no legal responsibility for possible consequences resulting from use of this registry protocol.

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KRANIOPHARYNGEOM Registry 2019 is most gratefully financially supported by the German Child Cancer Foundation, Bonn (www.kinderkrebsstiftung.de). Certification of KRANIOPHARYNGEOM Registry 2019 by the German Cancer Society (DKG) is in preparation.

According to the joint German federal committee (GBA) 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 oncological centers and have to be included in German Society of Pediatric Oncology and Hematology (GPOH) trials. Children and adolescents with craniopharynogioma were specifically included in this legal directive. The out-patient care of children and adolescents with craniopharynogioma during follow-up is not specifically affected by this GBA decision. KRANIOPHARYNGEOM Registry 2019 requests that all colleagues and specialists involved in the follow-up care of craniopharynogioma patients fully participate by registering all patients.

Patient agreement to be included in this study and allow transmission and processing of their data should be obtained early from parents and patients – either pre- or postoperatively.

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KRANIOPHARYNGEOM 2000/2007 trials - Summary 2001 - 2017

Craniopharyngioma are rare, dysontogenetic sellar region tumors. A German retrospective cross-sectional brain tumor study (**HIT-ENDO**) examined 306 child and adolescent craniopharyngioma patients regarding their prognoses. Even though a high overall survival rate of 92% was observed, quality of life (QoL) and functional capacity of the long-term survivors were compromised due to hypothalamic involvement of the tumor. Hypothalamic involvement was associated with eating disorders, severe hypothalamic obesity, high rates of neurosurgical interventions and comorbidities. Based on retrospective nature of HIT-ENDO data evaluation, neuroradiological assessment of tumor location and grading of hypothalamic involvement were difficult for the HIT-ENDO cohort.

The multicenter **KRANIOPHARYNGEOM 2000** surveillance study prospectively evaluated reference-confirmed data of 101 pediatric craniopharyngioma patients regarding their neuroradiological diagnostics, therapy and prognosis (QoL and functional capacity). Therapeutical recommendations and randomization were not included in the scope of KRANIOPHARYNGEOM 2000. The results of KRANIOPHARYNGEOM 2000 were as follows:

- Hypothalamus involvement in a craniopharyngioma tumor represents the most important risk factor for impaired long-term prognosis (QoL and functional capacity).
- The most significant increase in body mass index (BMI) resulting in long-term severe hypothalamic obesity occurs during the first 12 month after diagnosis/surgery.
- A radical excision is not recommended in cases of hypothalamus involvement with consideration of severe sequelae due to gross total resection.

KRANIOPHARYNGEOM 2007 analyzed by means of a randomized investigation, the optimal timing of postoperative irradiation (XRT) (immediate postoperative XRT vs. XRT in response to progression) in craniopharyngioma patients ≥ 5-year (yr). The primary endpoint of KRANIOPHARYNGEOM 2007 was patient QoL assessment measured by PedQol.
The duration of the study was subdivided into a phase running up until the interim analysis (IA), and the recruitment phase following IA – running up until the end analysis (EA). In 2016, the IA was carried out after recruitment of 20 randomized patients and an observation of over three yrs. The IA phase yielded little therapy-effecting results. Accordingly, the randomization was stopped in 2016.

KRANIOPHARYNGEOM Registry 2019 will prospectively collect and descriptively analyse data on diagnostics, treatment, and follow-up of patients with craniopharyngioma. In continuation of preceding studies also patients with xanthogranuloma, meningioma, pituitary adenpma, prolactinoma and cystic intracranial malformations will be registered.

The registry is open for collaborative projects and investigations.

KRANIOPHARYNGEOM Registry 2019 – Synopsis

Title: KRANIOPHARYNGEOM Registry 2019 - Multicenter registry for patients with childhood-onset craniopharyngioma, xanthogranuloma, cysts of Rathke's pouch, meningioma, pituitary adenoma, arachnoid cysts

Short Title: KRANIOPHARYNGEOM Registry 2019

Investigator: PD Dr. med. Carsten Friedrich, Universitätsklinik für Kinder- und Jugendmedizin, Klinikum Oldenburg AöR, Oldenburg

Topic: Childhood-onset craniopharyngioma, xanthogranuloma, cysts of Rathke's pouch, meningioma, pituitary adenoma, arachnoid cysts

Objectives:
- Collect epidemiological information
- Collect information on treatment and outcome to determine whether a relationship exists between outcomes and specific interventions
- Collect information on late effects and QoL
- Assess the quality of treatment by the means of data collection, data check and an advisory service provided by the registry and the reference centers
- Establishment of a tumor bank as a base for further biological studies to define new molecular risk factors and to identify new targets for therapy

Expected case numbers:

30 craniopharyngioma patients/yr
10 patients with other sellar masses/yr

Endpoints:
- Overall survival (OS)
- Progression-free survival (PFS)
- Quality of life (PedQol, PedsQL, FMH)
- Degree of obesity (BMI SDS)

Factors of influence (mandatory):
- Tumor location (grade of hypothalamic involvement, grade 0-2)
- Neurosurgical treatment strategy (intended radical resection vs. incomplete resection + XRT)
- Realized degree of surgical resection (complete resection vs. incomplete resection)
- Postsurgical hypothalamic lesions (grade 0-2)
- Irradiation: modality (photon vs. proton beam therapy) and treatment (dose)

Factors of influence (potential):
- Clinical manifestations and symptoms in history
- Duration of history
- Histology (adamantinomatous vs. papillary type)
- Hydrocephalus at diagnosis
- Patient load of treating neurosurgical units (based on patient load during 10 yrs)
- Tumor structure in imaging (total volume, cysts, calcifications)
- Endocrine deficiencies (number of deficient hypothalamic-pituitary axes)
- Growth hormone substitution (patient age at initiation, duration)
- Ophthalmological deficits (visual acuity, perimetric deficits)
- Neuropsychological findings, memory deficits, cognition (HIT-Basisdiagnostikum)
- Eating disorders (IEG)
- Experimental therapeutic approaches for obesity treatment (GLP-1R Agonists, Oxytocin)
- Other therapeutic approaches, i.e. intracavitary therapy (intracystic interferone α (INF–α))

Inclusion criteria:

Confirmed histological diagnosis of craniopharyngioma, xanthogranuloma, cysts of Rathke's pouch, meningioma, pituitary adenoma or arachnoid cysts in patients ≤18 yrs by reference pathology.
Informed consent by legal guardians and/or patient to contribute data to the registry.

Exclusion criteria:

Absence of informed consent by legal guardians and/or patient to contribute data to the registry.

Statistical methods:

The aim of the statistical analyses is to describe the frequency and modality of treatment approaches as well as diagnostic features and to investigate their influence on survival and QoL. The association between endpoints reflecting survival and QoL and a set of independent variables that represent diagnostic characteristics and treatment strategies will be analyzed. Descriptive and inferential methods appropriate to the distribution of the particular endpoint will be chosen (e.g. Kaplan-Meier estimator, log-rank test, Student's t-test, Mann-Whitney U-test). Since the planned study is observational, multivariable analysis strategies as Cox regression, linear regression or (linear) mixed model analyses are primarily used in addition to univariable analyses to enable adjusted analyses. All inferential analyses will be regarded as exploratory (hypotheses generating) and will be interpreted accordingly.

Ethical considerations:

The registry will be conducted in accordance with the Declaration of Helsinki, the current revision of ICH, and the local law.

KRANIOPHARYNGEOM Registry 2019 – Synopse

Titel: KRANIOPHARYNGEOM Registry 2019 - Multizentrisches Register für Kinder und Jugendliche mir Kraniopharyngeom, Xanthogranulom, Zysten der Rathkeschen Tasche, Meningeom, Hypophysenadenom, Arachnoidalzysten

Kurztitel: KRANIOPHARYNGEOM Registry 2019

Koordinator: PD Dr. med. Carsten Friedrich Universitätsklinik für Kinder- und Jugendmedizin, Klinikum Oldenburg AöR, Oldenburg

Thema: Kraniopharyngeom, Xanthogranulom, Zysten der Rathkeschen Tasche, Meningeom, Hypophysenadenom, Arachnoidalzysten im Kindes- und Jugendalter

Ziele:
- Sammlung epidemiologischer Daten
- Sammlung von Informationen zu Behandlung und Behandlungsergebnis sowie retrospektive Auswertung des Zusammenhangs zwischen Intervention und Ergebnis
- Erfassung von Spätfolgen und Lebensqualität
- Beurteilung der Qualität der Behandlung durch Datensammlung, Datenüberprüfung und Beratung durch das Registerzentrum und die Referenzeinrichtungen
- Schaffung einer Tumorbank als Grundlage für zukünftige biologische Forschungsvorhaben zur Identifizierung neuer Risikofaktoren und Angriffspunkte für zielgerichtete Therapeutika

Erwartete Fallzahlen:

30 Kraniopharyngeompatienten/Jahr
10 Patienten mit anderer sellären Raumforderungen/Jahr

Endpunkte:
- Gesamtüberleben
- Ereignisfreies Überleben
- Lebensqualität (PedQol, PedsQL, FMH)
- Grad der Adipositas (BMI SDS)

Einflussfaktoren (mandatory):
- Tumorlokalisation (Grad der Hypothalamus-Beteiligung, Grad 0-2)
- Neurochirurgische Strategie (intendierte radikale Resektion vs. inkomplette Resektion + XRT)
- Realisierter Grad der Resektion (komplette Resektion vs. inkomplette Resektion)
- Postoperative hypothalamische Läsionen (Grad 0-2)
- Strahlentherapie: Modalität (Photonen- vs. Protonenbestrahlung) und Behandlungsplanung (Dosis)

Einflussfaktoren (potentiell):
- Symptome in der Vorgeschichte
- Anamnesedauer
- Histologie (adamantinomatöser vs. papillärer Typ)
- Hydrocephalus bei Diagnosestellung
- Zentrumsgröße (basierend auf der Anzahl rekrutierter Patienten während 10 Jahren)
- Tumorstruktur in der Bildgebung (Tumorvolumen, Zysten, Verkalkungen)
- Endokrine Ausfälle (Anzahl der defizienten hypothalamisch-hypophysären Achsen)
- Wachstumshormonsubstitution (Alter bei Therapiebeginn, Therapiedauer)
- Opthalmologische Defizite (Visual acuity, Gesichtsfeldausfälle)
- Neuropsychologische Befunde, Gedächtnis, Kognition (HIT-Basisdiagnostikum)
- Störungen des Essverhaltens (IEG)
- Experimentelle Therapieansätze zur Adipositasbehandlung und Prävention (GLP-1R Agonisten, Oxytocin)
- Andere Therapieansätze wie z.B. intracavitäre Therapie (intrazystisches IFN–α)

Einschlusskriterien:

Referenzpathologisch bestätigte histologische Diagnose eines Kraniopharyngeoms, eines Xanthogranuloms, Zysten der Rathkeschen Tasche, eines Meningeoms, eines Hypophysenadenoms oder Arachnoidalzysten im Kindes- und Jugendalter (Alter bei Diagnose ≤ 18 Jahre).
Zustimmung (Informed consent) der gesetzlichen Vertreter und/oder des betroffenen Patienten zur Teilnahme am Register.

Ausschlusskriterien:

Fehlende oder widerrufene Zustimmung (Informed consent) der gesetzlichen Vertreter und/oder des betroffenen Patienten zur Teilnahme am Register.

Statistische Methoden:

Ziel der statistischen Analysen ist es, Häufigkeit und Modalität verschiedener Behandlungsansätzen sowie diagnostischer Kriterien zu beschreiben und ihren Einfluss auf das Überleben und die Lebensqualität zu untersuchen. Der Zusammenhang zwischen Endpunkten, die das Überleben und die Lebensqualität widerspiegeln, und einer Reihe von unabhängigen Variablen, die diagnostische Merkmale und Behandlungsstrategien darstellen, wird analysiert. Entsprechend der Verteilung des jeweiligen Endpunktes werden geeignete deskriptive und inferenzstatistische Methoden verwendet (z.B. Kaplan-Meier-Schätzer, Log-Rank-Test, Student's t-Test, Mann-Whitney U-Test). Da es sich um eine reine Beobachtungsstudie handelt, werden neben univariablen Analysen vorrangig multivariable Analysestrategien wie z.B. Cox-Regression, lineare Regression oder (lineare) gemischte Modelle eingesetzt, um adjustierte Analysen zu ermöglichen. Alle Analysen werden als explorativ (d.h. hypothesengenerierend) erachtet und entsprechend interpretiert.

Ethikrichtlinien:

Das vorliegende Register wird gemäß der geltenden gesetzlichen Bestimmungen und Richtlinien sowie der aktuellen Richtlinie der International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH-Richtlinie) für GCP (Good Clinical Practice) durchgeführt. Die Richtlinien der Deklaration von Helsinki werden eingehalten.

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1. Introduction

Craniopharyngiomas are rare, dysontogenic midline tumors, actually embryogenic malformations from ectoblastic remnants of Rathke's pouch. They are usually cystic, occasionally solid, sometime mixed (solid/cystic) and are nonmalignant. The adamantinomatous 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 diagnosed with clinical presentation of neurological and/or brain pressure symptoms and are frequently diagnosed via endocrinological disorders (growth hormone deficiency, central diabetes insipidus (DI), hypogonadism and obesity) and/or by the ophthalmologic disorder bitemporal hemianopsia. A suspected craniopharyngioma diagnosis is confirmed and histologically characterized using craniopharyngioma tumor imaging criteria.

It is the task of an experienced, multidisciplinary team of neurosurgeons, neuroradiologists and radiology therapists to decide on the appropriate treatment strategy regarding surgical approach and intraoperative attainable degree of resection (primary intentions being complete resection, incomplete resection, cyst decompression, irradiation therapy). Individual, risk-adapted treatment strategies are highly justifiable as prognosis is based on the patient's sequelae. Endocrine deficiencies, hormonal substitution therapy, extreme obesity from hypothalamic-related eating disorders, visual impairment, and neurological and neuropsychiatric disturbances affect postoperative morbidity and therefore craniopharyngioma patients' QoL. The first 12 month after primary diagnosis/ surgery are the crucial period for the development and clinical appearance of sequelae such as hypothalamic obesity and neuropsychological deficits.
However, in patients with hypothalamic tumor involvement it could be demonstrated that the pre-treatment tumor extension to hypothalamic structures has major apriori impact on prognosis and sequelae. In these patients with hypothalamic lesions, risk-adapted treatment strategies have to be focussed on prevention of further deterioration of pre-existing hypothalamus-related sequelae.

The present protocol is a prospective, multicenter registry evaluating childhood-onset craniopharyngioma patients' prognoses and outcome with regard to diagnostic characteristics, chosen treatment strategies and modalities, and following-up care.

2. Background

2.1. Embryology

It was the 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 yrs 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 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 purports 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 [1-3].

2.2. Pathology and molecular biology

Adamantinomatous 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 adamantinomatous craniopharyngioma cysts consist of a cholesterol-rich, brownish-yellow oily fluid with partially firm components. The squamous papillary cyst fluid is less oily [3].
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 gliotic tissue, the adamantinomatous craniopharyngiomas in particular display multiple tumorous invasions into the adjacent brain tissue that frequently cannot be removed by microsurgical complete resection. Controlling for degree of resection, the two histological variants (adamantinomatous vs. squamous papillary) demonstrate no differences in recurrence rates [4].
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.
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 histopathological investigations reveal that xanthogranulom is a histologically discrete, sellar-region entity occurring especially in adolescents and young adults. Its more favorable prognosis is a consequence of the intra-sellar tumor localization, smaller volume and superior surgical resectability. Non-adamantinomatous epithelium tubular structures are histologically localized, whereas adamantinomatous epitheliums are typically absent of xanthogranulon and found in less than 10% of cases.

It is now well established that the vast majority, very likely all, of the human adamantinomatous craniopharyngioma tumors carry over-activating mutations in the gene encoding β-catenin (*CTNNB1*) [5-8]. Of note, the papillary form of craniopharyngioma, which usually present in the elderly, carry *BRAF p.V600E* mutations and show distinct methylation profiles, indicating that adamantinomatous craniopharyngioma and papillary craniopharyngioma have two different molecular identities [8, 9]. Recently, the coexistence of *BRAF p.V600E* and *CTNNB1* mutations have been reported in one case of adamantinomatous craniopharyngioma [10]. Further molecular analyses are required to identify which, if any, other recurrent mutations are present in human adamantinomatous craniopharyngioma in addition to those in *CTNNB1*. Nonetheless, it seems likely that human adamantinomatous craniopharyngioma is a tumor with a low mutation burden [3].
Most of the identified mutations in adamantinomatous craniopharyngioma lie in regulatory amino aids encoded by exon 3 of the *CTNNB1* gene [11]. The molecular consequence of such mutations is the expression of a mutant form of β-catenin with increased degradation resistance, resulting in the accumulation of β-catenin and subsequent activation of the WNT pathway. Confirming this, human adamantinomatous craniopharyngioma contains cells with nucleo-cytoplasmic accumulation of β-catenin, which are either dispersed throughout the tumors or grouped in whorls of cells, termed cell

clusters [12-14]. These clusters are not present in any other pituitary tumor and represent a histological hallmark of human adamantinomatous craniopharyngioma [15]. Tumor cells including cell clusters, activate the WNT pathway, as evidenced by the expression of gene targets such as *AXIN2* or *LEF1 [12, 13]*.

A genetically engineered mouse model (GEMM) has been generated by expressing a mutant form of β-catenin that is resistant to degradation in undifferentiated embryonic precursors of the pituitary gland (i.e. the embryonic adamantinomatous craniopharyngioma mouse model) [12]. Interestingly, when oncogenic β-catenin is expressed in committed progenitors (e.g. *Pit1*-expressing cells) or hormone-producing cells (e.g. somatotrophs), no tumors develop, suggesting that only undifferentiated progenitors provide the cellular context required for tumors to form. This oncogenic β-catenin is functionally equivalent to that identified in human adamantinomatous craniopharyngioma, therefore the molecular aetiology in this GEMM is similar to human adamantinomatous craniopharyngioma.
Several histological and molecular features are conserved between the mouse and human tumors. As observed in humans, mouse tumors show cystic and solid components, are synaptophysin-negative and do not express hormones. The pituitary gland of these mice at birth and early postnatal stages show the presence of clusters with nucleo-cytoplasmic accumulation of beta-catenin, which typifies human adamantinomatous craniopharyngioma. However, murine tumors do not show a clear palisading epithelium, wet keratin or any sign of calcification, all common features in human tumors. Likewise, tumors do not infiltrate the brain or visual pathways in the mouse, but this is a common finding in humans. Despite the histological differences, molecular analyses of the mouse tumors have predicted the up-regulation of several gene pathways in the human, which have been later confirmed in human studies (e.g. SHH and C-X-C motif chemokine receptor CXCR4) [16-18]. Therefore, this model shows similar molecular aetiology and pathogenesis to human adamantinomatous craniopharyngioma, but there are species-specific differences that need to be considered [19].

2.3. Epidemiology

Craniopharyngioma is the most common nonglial intracranial tumor in the pediatric population with an incidence rate of 0.5–2 per million people per yr, 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 yrs of age and adults 50 to 75 yrs of age [20]. Craniopharyngiomas are systematically recorded by the German Pediatric Cancer Registry (DKKR) in accordance with international guidelines. Between 1980 and 2001, 385 craniopharyngioma patients under the age of 18 were identified and registered. Of that total, 345 diagnosed patients were <15 yrs of age. The median age at the time of diagnosis was 8.6 yrs in this under 15-yrs-of-age patient group (sex ratio 1:1). Their overal survival rate was 93% after 3 yrs of observation, 91% after 5 yrs, and 87% after 10 yrs of observation. Patients who were diagnosed and treated in the 1980s had a lower survival rate probability ($p<0.05$) than patients who were diagnosed and treated in the 1990s (5-yr survival rate probability: 88% vs. 96% respectively) [4].

2.4. Anatomical localization

The most frequent location is suprasellar with an intrasellar component as well. Around 20% of craniopharyngiomas are exclusively suprasellar and approximately 5% are exclusively intrasellar [21]. A tumor invasion into the anterior cranial fossa is found in 30% of cases, while 23% expand into the middle cranial fossa. Rare, ectopic locations occur at the sphenoid bone, pharynx and cerebellopontine angle. Papillary type craniopharyngioma growths are often found in the 3rd ventricle. In 20% of the cases with retroclival expansion, expansions consist of solid tumor components.

2.5. Clinical symptoms

The diagnosis of childhood craniopharyngioma is often made late - sometimes yrs after the initial appearance of symptoms - and the clinical picture at the time of diagnosis is often dominated by non-specific manifestations of intracranial pressure (e.g., headache and nausea) (**Figure 1**). Further primary manifestations are visual impairment (62-84%) and endocrine deficits (52-87%). Endocrine deficits are frequently caused by disturbances to the hypothalamic–pituitary axes that affect growth hormone secretion (75%), gonadotropins (40%), adrenocorticotropic hormone (ACTH) (25%), and thyroid-stimulating hormone (TSH) (25%). At the time of diagnosis, 40 to 87% of patients present with at least one hormonal deficit [22-24], and other endocrine symptoms such as neurohormonal DI are present preoperatively in 17 to 27% of patients [23-25]. An analysis of anthropometric data obtained in routine checkups before the diagnosis of craniopharyngioma in 90 children [26] revealed that a pathologically

reduced growth rate - an early manifestation of the disease - presents in patients as young as 12 month, but that significant weight gain, predictive of hypothalamic obesity, tends to occur as a later manifestation, shortly before diagnosis. In a study of Hoffmann *et al*. [27], median duration of history was 6 months (range: 0.1–108 mo) and correlated positively with age at diagnosis. Tumor size, hypothalamic involvement, degree of resection, and BMI at diagnosis were not related to duration of history. In multivariate analysis adjusted for age at diagnosis, only hydrocephalus was found to have a significant influence on duration of history. Visual and neurological deficits were associated with larger initial tumor size and impaired 10-yr overall survival (OS). Weight gain and growth failure were observed with longest duration of history. Progression-free survival (PFS) and functional capacity were not related to any specific symptom. Endocrine deficits at diagnosis were associated with long duration of history [27]. The combination of the symptoms - headches, impaired vision, growth retardation and polyuria / polydipsia - should arouse suspicion of craniopharyngioma.

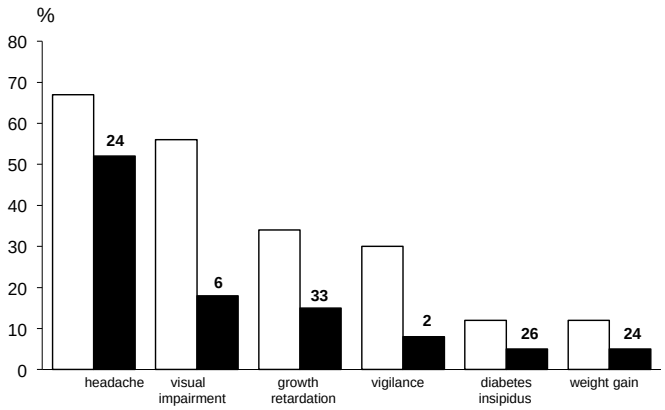

Figure 1: Manifestations before diagnosis of craniopharyngioma in children and adolescents. Frequency of occurrence of each manifestation before diagnosis (open columns) and frequency of occurrence as the initial manifestation (black columns). The median time (month = mo) from the appearance of each initial manifestation until diagnosis is indicated above each black column. In the overall group, the median time from the initial manifestation of disease until diagnosis was 12 mo, with a range of 0.01 to 96 mo. Modified from [28], with kind permission of Springer.

2.6. Imaging diagnostics

Both computerized tomography (CT) and magnetic resonance imaging (MRI) reveal that craniopharyngioma is typically a cystic tumor of the intra- and/or suprasellar region. The most common localization is suprasellar, with an intrasellar portion; only 20% are exclusively suprasellar and even less (5%) exclusively intrasellar [29-32]. CT is the only way to definitively detect or exclude calcifications in craniopharyngioma tissue, which is found in approximately 90% of these tumors. The signal intensity of craniopharyngioma in MRI is highly variable because it depends on the protein concentration of the cystic fluid. Solid tumor portions and cyst membranes appear isointense in T1-weighted MRI, often with a mildly heterogeneous structure. The combination of solid, cystic, and calcified tumor components is an important radiological clue to the diagnosis. The differential diagnosis in imaging of sellar masses include hypothalamic glioma and optic glioma, Langerhans cell histiocytosis (LCH), Rathke's cleft cyst, xanthogranuloma, intracranial germinoma, epidermoid tumor, thrombosis of arachnoid cysts, colloidal cyst of the 3rd ventricle, pituitary adenoma, an aneurysm, and rare inflammatory variations [29, 33].
MRI before and after contrast application (gadolinium) is the standard imaging for detection of craniopharyngioma, further imaged by native CT to detect calcifications [29]. After preoperative detection of calcifications and complete resection confirmed by postoperative MRI, a post-surgical native CT of the sellar/parasellar area (without contrast medium application) is recommended for definitive confirmation of complete resection [29]. The use of heavily T2-weighted MRI [34] and FIESTA (fast imaging employing steady-state acquisistion) MRI sequences [35] allow an optimal identification of the brain-craniopharyngioma interphase as well as the relative position of the hypothalamus both essential for the planning of surgical/radiotherapy treatments. Imaging for detection of relapse or progression

during follow-up should be confined to MRI in order to increase diagnostic sensitivity and to decrease radiation burden.
The differential diagnosis of craniopharyngioma includes: pituitary adenoma, hypothalamic glioma and glioma of the chiasma, optical tract and optical nerves, Rathke cleft cysts, epidermoid tumors, germinomas, Langerhans histicytosis, aneurysmata, arachnoid cysts, inflammatory masses, and colloid cysts of the 3rd ventricle.

2.7. Natural course of disease

Craniopharyngiomas histologically consist of differentiated tissue of low-grade malignancy. The clinical course of this tumor type is characterized by its capacity to infiltrate surrounding normal tissue due to its location near the hypothalamic-pituitary axes structures as well as the optic nerve and chiasm. The prognosis is unfavourable without therapy.

2.8. Treatment stategies

2.8.1. Neurosurgery

2.8.1.1. Strategies and effects

For favorably localized craniopharyngioma (i.e., without involvement of hypothalamic or optical structures), the preferred treatment of choice is an attempt at complete resection with preservation of visual and hypothalamic function [36-39]. For unfavorably localized tumors too close to or entangled with the optic nerve and/or the hypothalamus, controversy exists over whether complete resection should still be attempted or whether a planned limited resection (biopsy, partial/subtotal resection) should be performed [39-41]. Many authors take a critical view of planned radical resection in these cases because of the risk of surgically-induced deficits (mainly hypothalamic) and the high rate of recurrence in infants and small children despite apparently complete resection [42, 43]. Recurrences at ectopic locations are reported [44]. Whereas following incomplete resection the residual tumor shows progression in 71 to 90% of patients, the rate of progression after incomplete resection followed by radiotherapy is 21% [45]. Elowe-Gruau and coworkers recently published the results of a single institution study at Necker Enfants-Malades Teaching Hospital, Paris, France, showing that a hypothalamus-sparing surgical strategy combined with postsurgical radiotherapy decreased the rate of severe long-term obesity in survivors without increasing their risk for local relapses when compared with a historical cohort treated before 2002 at the same experienced institution with a radical surgical approach [46].
However, the published literature to date [25, 42, 46-52] has not settled the controversy over the best treatment strategy for craniopharyngioma (intended primary gross total resection, versus biopsy/partial resection followed by irradiation). Therapeutic consequences of surgery and irradiation also remain a matter of debate. Above all, effects of the chosen treatment sequence (immediate irradiation vs. progression-contingent irradiation of residual tumor) on QoL are not clearly characterized based on the retrospective data published to date. A retrospective analysis sited primary therapy FSIQ (Full Scale Intelligence Quotient) losses of 9.8 points after a single complete resection compared to a loss of 1.25 points after limited resection followed by radiation therapy [52]. For a second surgical intervention carried out following a relapse, the loss was 13.1 points, statistically suggesting that radical and/or repeated surgeries seem to generate negative influences on neurocognitive functions compared to limited surgical intervention plus immediate irradiation treatment. However, only very limited available retrospective data exists.

Endoscopic procedures are usually considered in occlusive hydrocephalus caused by tumor cysts of the foramen of Monro (FOM) [53]. The small size of instruments insertable through the working canals of the endoscope allows biopsies of the tumor and prevents larger resections. The standard access is a paramedian frontal burr hole in front of the coronal suture [37]. After transcortical puncture of the lateral ventricle, the endoscope can be moved inside the inner cerebrospinal fluid (CSF) space through the FOM within some limits. Besides cyst punctures and biopsies [54], catheters can be placed under optic control.

2.8.1.2. Transcranial approach

The treatment of craniopharyngiomas with suprasellar extension can be performed via transcranial approaches. Craniopharyngiomas arising from the pituitary stalk and those tumors extending into the infundibulum with the potential risk of severe surgical lesions can be reached by a classical pterional or

subfrontal route [55, 56]. Limitations are that the optic chiasm/optic nerves usually lay in front of the tumor, hindering surgical access. Also, the identification of the pituitary stalk can be difficult and therefore at high risk of surgical lesions. Tumors extending into the 3rd ventricle can be reached by opening of the lamina terminalis behind the optic chiasm [57]. Tumor cysts can be opened for removal of the cyst wall or solid parts and decompression. Another approach for large tumors within the ventricle is the transventricular route through a lateral ventricle and the FOM [58]. This approach may be considered in obstructive hydrocephalus. Retrosigmoid approaches for uncommon posterior fossa tumor extensions are rarely necessary. In all cases of incomplete tumor removal during transcranial procedures, catheters connected with, for instance, a Rickham reservoir can be inserted into remaining cysts for later aspiration of cyst fluid or instillation of sclerosing substances.

2.8.1.3. Transsphenoidal approach

Regarding the surgical access strategy, it is generally accepted that the transsphenoidal approach is the first choice in infradiaphragmatic craniopharyngiomas with sellar enlargement [59, 60]. Several reports of extended approaches to suprasellar craniopharyngiomas have been published [60-62]. These extended transsphenoidal approaches for supradiaphragmatic tumors are associated with a different incidence of endocrinopathies and neurological complications when compared to infradiaphragmatic lesions, especially when complete or gross total resection is attempted [62]. CSF fistulas are another complication, which require a meticulous technique to prevent. It is important to mention that success in choosing the correct approach as well as any subsequent surgical complications during resection have been shown in follow-up studies to be associated with the experience of the surgeon [33, 63, 64]. In comparison to transcranial procedures, potential advantages of transsphenoidal approaches include the avoidance of craniotomy and brain retraction and reduced neurovascular manipulation [65].

2.9. Irradiation

The combinationof limited (hypothalamus-sparing) surgical strategy (2.8.1.1) and postoperative irradiation is favored as it has been proven to archieve similar long-term control rates whem comepared with gross-total resection [66].

KRANIOPHARYNGEOM Registry 2019 is a prospective, multicenter registry assessing the results when treating craniopharyngioma patients with various current therapy strategies. The registry does not include details on radiotherapy with regard to treatment technique, target volume definition and dose prescription. Therefore, a radiotherapy guideline was established and provides detailed recommendations for more conformal fractionated radiotherapy.

2.9.1. Conventional external radiotherapy

Technology	Advantages	Disadvantages
Conventional 2-D radiotherapy	Reliable clinical data and long follow-up indicating high efficacy of radiotherapy	Poor geometrical precision. No reliable protection of normal surrounding tissue
Fractionated conformal radiation therapy/IMRT	Excellent adjustment of treatment portals to tumor site. In 3-D. Sparing of normal tissue	Rigid head fixation (relocatable). Few patient numbers and not yet long follow-up
Fractionated proton therapy	Optimal coverage of tumor site. With maximal sparing of surrounding tissue	Few patient numbers. Limited access, high costs
Radiosurgery	Only one session. Excellent coverage of tumor. Almost no dose to non-target tissue	Limited clinical settings. Tumor control inferior to fractionated treatments? Low patient numbers. No long follow-up
Hypofractionated image guided radiosurgery (CyberKnife)	Only few sessions. The biological advantages of fractionation can be utilized. Excellent coverage of tumor. Almost no dose to non-target tissue	Very few experiences. Role still unclear. No reliable data for tumor control. No long-term follow-up. Only selected clinical settings
Intracavitary colloid isotope application	High tumor control rates for cystic components	Only cystic tumors. Underdosage in solid components. Leak-age possible. Detrimental effects on visual function reported

Interstitial irradiation (Iodine seeds)	Excellent dose conformity. Optimal protection of normal tissue	Very few clinical data

The site and rate of progression of craniopharyngioma, as well as the patient's age, are important considerations when deciding whether reoperation and/or radiotherapy should be performed. Craniopharyngiomas are usually sharply bordered in the imaging. In contrast to primary brain tumors, they tend towards less infiltrative growth, permitting a small safety margin of 5 mm maximum [67, 68]. These biological characteristics usually allow the option of using high-precision, three-dimensional conformation technology. A conventional, fractionated irradiation target (total) volume dose of 54 Gy (International Commisssion on Radiation Units and Measurements Report 50 ($ICRU_{50}$) / $ICRU_{83}$) has been established worldwide [45, 52, 67-77].

Table 1: Advantgaes and disadvantages of modern radiotherapy methods used in the treatment of craniopharyngioma (Müller *et al.*, Nat Rev Endocrinol, 2017) [3].

An excellent long-term outcome of conventional radiotherapy was found in many retrospective series [1, 50, 51, 78-82] reporting 10 and 20 yrs progression-free survival up to 95 and 54%. Advances in radiotherapeutic technologies have opened up new approaches in the radiooncological management of craniopharyngioma (**Table 1**). The selection of the adequate treatment technology is an ongoing debate. Latest literature shows that with the use of modern imaging technologies and treatment planning systems, a precise coverage of the tumor area can be achieved by using stereotactic irradiation technologies [83-87]. More recently also Proton beam therapy has been established for craniopharyngioma [87, 88, 90-92]. If a cystic component is present, careful monitoring during radiotherapy is necessary because changes and even enlargements in cystic volume are possible during irradiation [88]. Therefore, 3-D imaging as regular CT-scans, i.e. every two weeks, are recommended in order to investigate the need for adaptive radiotherapy treatment planning.

2.9.2. Proton beam therapy

Proton beams have an "inverse dose profile" across the tissues, whereby the dose released by the particles increases with penetration depth until reaching a maximum at the end of the particle range (Bragg peak). Beyond the Bragg peak, practically no dose is deposited. Fitzek and colleagues published the first series of 15 craniopharyngioma patients treated with combined proton-photon irradiation for residual or recurrent disease [89]. Actuarial 5- and 10-yr local control rates were 93% and 85%, respectively, with 10-yr survival expectancy in 72% of patients. No treatment-related neurocognitive deficits were reported; functional status, academic skills and professional abilities were unaltered after proton beam therapy. Luu and colleagues published a preliminary report in 2006 on 16 patients treated with proton beam therapy [90]. Local tumor control was achieved in 14 of 16 (87.5%) patients. During follow-up (12 to 121 month later), late sequelae included newly diagnosed panhypopituitarism, a cerebrovascular accident and an out-of-proton-field posterior fossa meningioma (59 month following proton beam therapy administered to patient who previously received photon radiotherapy). One study of proton beam therapy in craniopharyngioma assessed cyst growth during the treatment course: 24% of patients demonstrated cyst enlargement and 5% cyst reduction requiring modification of the treatment plan, while one patient required cyst drainage during treatment [88].
Clinical outcome data are still very limited for assessing the value of proton beam therapy compared to modern photon therapy, as the technique is available in only a few centers. However, proton beam therapy has the potential advantages of better conformation of dose to the target volume, sparing of critical structures, reduced integral dose, and lower dose of secondary neutrons, which should reduce the risk of secondary malignancies [91-93]. As proton beam therapy becomes more available, additional data on this promising therapy is expected.

2.9.3. Stereotactic radiotherapy

Stereotactic radiotherapy (SRT) can be given in a single fraction (stereotactic radiosuergery) or in multiple doses (fractionated stereotactic radiotherapy). SRT permits a highly conformal dose distribution and delivery to the tumor and provide a steep dose gradient to surrounding normal tissue.
SRT is a modality combining the accurate focal dose delivery of stereotactic radiosurgery with the radiobiological advantages of fractionation [83]. It requires sophisticated treatment planning systems, a dedicated high-energy linear accelerator, and stereotactic mobilization devices. Compared with conventional irradiation, it adopts reduced safety margins and offers optimal sparing of the normal tissue surrounding the tumor, thereby possibly minimizing the acute and long-term toxicities of irradiation [75,

94, 95].
The data on the usefulness of SRT for the management of craniopharyngiomas are limited, but the larger series published thus far provide promising results [94, 95]. The median target dose reported was 52.2 Gy with conventional fractionation and a safety margin of 2 mm. The 10-yr actuarial local control and overall survival rates were 100 and 83%, respectively. Side effects included mild acute toxicity and two patients developed initial enlargement of the cystic component, necessitating stereotactic aspiration in one patient. Reported median (4 yrs) follow-ups (7 month to 12 yrs) revealed 16.6% of subjects developed impaired pituitary function; no deterioration of vision, radionecrosis, or second malignancies were observed.

2.9.4. Radiosurgery

The most frequently used system for delivery of single fraction radiotherapy is gamma knife [96]. Gamma knife requires the patient to be immobilized using a stereotactic fixed frame, delivering the treatment in a single radiosurgery session. Generally, patients treated with radiosurgery had small (<3 cm), mainly solid tumors, which were well circumscribed on imaging and sited >3 mm away from critical structures such as brainstem, optic chiasm and optic nerves. Dose constraints for radiosurgery applied to the optic chiasm and brain stem were 8 to 9 Gy and 12 to 14 Gy, respectively [97-104]. In published gamma knife series, tumor control rates ranged from 67 to 94%. Rates of complications directly attributable to gamma knife radiosurgery ranged from 0 to 38%, including visual deterioration (0–38%), endocrine morbidity (0–19%) and neurological complications (0–2%). No treatment-related mortality has been reported [97, 99, 100].

2.9.5. Intracavitary β irradiation

Intracavitary β irradiation (brachytherapy) is a minimally invasive management strategy, first reported by Leksell and Liden in 1952 [105]. It involves stereotactically guided instillation of β-emitting isotopes into cystic craniopharyngiomas, delivering higher radiation doses to the cyst lining than the ones offered by conventional external beam irradiation. The beneficial effect is achieved through destruction of the secretory epithelial lining, causing elimination of the fluid production and cyst shrinkage [106, 107]. Subsequent studies assessed the efficacy of various β- and γ-emitting isotopes (mainly ^{32}P, ^{90}Y, ^{186}Re, and ^{198}Au) [108-115]; because none of them has the ideal physical and biological profile (i.e., pure β-emitter with short half-life and with tissue penetrance limited to cover only the cyst wall [114]), there is no consensus on which therapeutic agent is the most suitable. ^{90}Y has the shortest physical half-life (2.67 days (d)) but the greatest maximum β-energy (2.27 MeV) and half-value tissue penetrance (1.1 mm), thereby exposing critical structures to higher doses of irradiation [112]. ^{32}P is a pure β-emitting radionuclide but with a long half-life (14.3 d) [114]. Both ^{186}Re and ^{198}Au emit a considerable amount of γ-radiation [112].
Stereotactic instillation of radioisotopes has been discussed as an alternative therapeutic option, mainly for monocystic craniopharyngioma recurrences. Nevertheless, this treatment method is restricted to cystic craniopharyngioma and due to its limitations should be considered only for postoperative recurrences and after percutaneous irradiation [45, 116-119]. Prior to injection of the chosen agent, it must be confirmed that no leakage into the subarachnoid space is possible. Severe complications such as infection, bleeding, neurological damage due to leakage of radioisotopes and detrimental effects on visual function have been reported [120]. A non-randomized retrospective monocentric analysis showed that patients treated with less invasive stereotactic and radiooncological methods have a more favorable long-term clinical outcome compared to children treated with a more radical microsurgical approach [94].

2.10. Chemotherapy

2.10.1. Instillation of sclerosing substances for cystic tumors

An insertion of a catheter into a cystic craniopharyngioma is reported to prevail over the transient success of a cyst fenestration by allowing repetitive drainage of the tumor cyst and the opportunity of instillation of intracystic substances. Different neurosurgical techniques are employed for the placement of catheters. Even though it usually relieves pressure transiently, it is a useful therapeutic method for cystic recurrent tumors whose anatomical configuration and localization makes them difficult to resect [121, 122]. The instillation of sclerosing substances in craniopharyngioma cysts, such as bleomycin, using an intracystic catheter implanted by a stereotactic or open procedure has been used in such cases [94, 123-129]. Severe neurotoxic side effects were observed in some cases due to cystic leakage of bleomycin into cerebrospinal fluid [130]. Accordingly, a thorough neuroradiological imaging for exclusion

of cystic leakage is warranted before instillation of bleomycin.
Intracystic instillation of IFN–α was first used by Cavalheiro and colleagues, who have published the most experiences in treating cystic childhood craniopharyngiomas [131, 132]. Their latest publication [132] included 60 children with a mean age of 11 yrs, treated at three different institutions from 2000 to 2009. Twenty-nine of the 60 patients received intracystic IFN–α after initial surgery or after bleomycin treatment had failed; the remaining 31 were treated with IFN–α as a first-line treatment. While in 47 children (78%) more than 50% cyst shrinkage was achieved at completion of therapy, 13 children progressed and required surgical intervention. Only one-third of the patients experienced side effects such as headaches, palpebral edema, fever, chronic fatigue, or arthritis - none of which necessitated discontinuation of treatment - and there were no mortalities. Based on these reports on the effect and tolerability of IFN–α, its intracystic instillation is a promising therapeutic option for predominantly monocystic craniopharyngiomas [132-134].

2.11. Long-term outcome and sequelae

2.11.1. Morbidities

2.11.1.1. Pituitary deficiencies

Pituitary hormone deficiencies are common in craniopharyngioma. At the time of diagnosis, 40 to 87% of children [22-24, 135] present with at least one hormonal deficit and 17 to 27% [23, 24, 136] have been reported to have DI neurohormonalis. The rate of post-surgical pituitary hormone deficiencies increases due to the tumor's proximity or even involvement with the hypothalamic–pituitary axes [22, 24, 26, 52, 136-139]. Transient post-surgical DI occurs in up to 80 to 100% of all cases [22, 140]. The rate of permanent post-surgical DI ranges between 40 to 93% [22, 24, 52, 64, 136, 139-142].
In adult onset craniopharyngioma patients anterior pituitary deficiencies and DI are most common and the majority of patients present with hypopituitarism [48, 135, 143, 144]. Endocrine dysfunction may worsen upon treatment. Mortini *et al.* [145] reported that 82%, 76%, 73%, and 67% of adult onset craniopharyngioma patients with normal baseline values for GH , ACTH, TSH, and gonadotropins developed a new deficiency of the respective pituitary axis after surgery. Post-surgical onset of DI was observed in 70% of their patients. The risk for new endocrine deficits appears to be lower after transsphenoidal surgical approach [135, 145]. Recovery of preexisting pituitary dysfunction after surgery is rare. Most of the adult onset craniopharyngioma patients suffer from partial or complete hypopituitarism as well as DI, with approximately 80% requiring the substitution of more than two pituitary hormones [143, 146].
Growth hormone deficiency has been described at the time of diagnosis in 26 to 75% of childhood craniopharyngioma [23, 142], and impaired growth, one of the primary manifestations of craniopharyngioma, often occurs yrs before diagnosis [26]. Growth hormone deficiency following tumor treatment for childhood craniopharyngioma is found in about 70 to 92% of patients [26, 64, 147, 148] and a positive response to growth hormone treatment is seen in most cases [149]. Normal growth in childhood craniopharyngioma patients with proven growth hormone deficiency is reported in the literature [150]. In fact, childhood craniopharyngioma patients with hypothalamic involvement were found to achieve normal adult height more often than those without hypothalamic involvement [26]. Even though this phenomenon of "growth without growth hormone" was described in childhood craniopharyngioma almost five decades ago [151], the physiology of growth in these cases is still not fully understood, although insulin and/or leptin are suspected to play a compensating role in this phenomenon. Both of these hormones have been hypothesized to induce growth in the fetus and in obese children [152-154], with leptin reported to function as a bone growth factor acting directly at the level of bone growth centers, independently of growth hormone [152]. Mechanisms by which insulin stimulates growth include its known anabolic effects. At high serum levels, insulin may bind to the type 1 insulin-like growth factor (IGF) receptor and induce growth, mediated by its actions to decrease IGF-binding protein 1 levels, resulting in increased levels of free IGF-1 [152]. In support of this theory, obese childhood craniopharyngioma patients were found to present with higher height SDS (standard deviation score) at the time of diagnosis and at last follow-up with no difference in hormonal substitution, including growth hormone [155]. In contrast, another study found that childhood craniopharyngioma patients who were growing despite growth hormone deficiency had the same mean anthropometrical measures, body composition and metabolic indexes, including insulin levels, as those requiring growth hormone substitution [150].

2.11.1.2. Visual and neurological outcomes

Due to frequent suprasellar tumor localization, visual deficits (both visual acuity and visual fields) are relatively common in patients with craniopharyngioma: visual impairment as an initial clinical manifestation of craniopharyngioma is found in more than half of the affected patients [23], with some post-surgical improvement of vision in 41 to 48% of patients [22, 141]. Risk factors for post-surgical visual impairment include tumor location in the prechiasmatic area and severe pre-surgical visual deficits [22, 137]. Improved ophthalmological outcome has been detected in surgical cases using the transsphenoidal approach [141], but such an approach is limited to resection of mainly intrasellar tumors. Because most pediatric craniopharyngiomas typically extend to the suprasellar area, they are best removed through a transcranial or a combined transcranial and transsphenoidal approach.
Neurological sequelae include hemiparesis, epilepsy, cranial nerve deficits, and cerebrovascular disease manifestations [52, 136, 148]. Most of these sequelae are transient and the total prevalence of long-term neurological complications is reported to be 8% [22], but increases to 36% for large-sized tumors [136] and 30% when including both visual and neurological complications [140].

2.11.1.3. Hypothalamic dysfunction

Symptoms related to hypothalamic dysfunction, such as obesity, behavioral changes, disturbed circadian rhythm, sleep irregularities, daytime sleepiness, and imbalances in regulation of body temperature, thirst, heart rate and/or blood pressure have been found at diagnosis in 35% of childhood craniopharyngioma patients [136]. The rate of hypothalamic dysfunction dramatically increases following radical surgical treatment - in some series up to 65 to 80% [136, 140]. Even though pre-surgical evaluation of hypothalamic damage is difficult, both clinically and radiologically [137], tumor involvement of the 3rd ventricle or obstructive hydrocephalus are suggestive findings [22]. A three-level clinical grading system for hypothalamic dysfunction has been suggested based on the degree of obesity and hypothalamic tumor involvement [139].
Associated with high morbidity, suprachiasmatic lesions with hypothalamic involvement are difficult to treat. Surgical removal of tumor tissue beyond the mammillary bodies (i.e., in the posterior hypothalamic area) endangers hypothalamic structures and may cause hypothalamic obesity [40, 64]. With the aid of imaging studies, several reports have indicated that the degree of obesity of affected childhood craniopharyngioma patients is positively correlated with the degree and extent of hypothalamic damage [64, 156-158]. Fjalldal *et al.* [159] recently published the results of a cross sectional study of 42 patients who were analyzed for cognitive performance and psychosocial health at a median follow-up of 20 yrs (1 to 40 yrs) after diagnosis of childhood craniopharyngioma. The authors observed disturbed attention and impaired processing speed in craniopharyngioma patients; not surprisingly, the deficits were most pronounced in patients with hypothalamic involvement of childhood-onset craniopharyngioma [159]. Taking these considerations into account, a novel classification of pre-surgical involvement and post-surgical lesions of hypothalamic structures based on magnetic resonance imaging has been recently published [37]. The classification is intended to help establish more risk adapted surgical strategies based on a grading of pre-surgical hypothalamic involvement and postsurgical hypothalamic lesions.

2.11.1.4. Obesity and eating disorders

Rapid weight gain and severe obesity are the most perplexing complications due to hypothalamic involvement and/or treatment-related hypothalamic damage in craniopharyngioma patients. Weight gain in childhood craniopharyngioma patients often occurs yrs before diagnosis [26], with 12 to 19% of patients reported to be obese at diagnosis [23, 24, 140, 142]. Weight gain occurs despite adequate endocrine replacement of pituitary hormone deficiencies. The hypothalamic disturbance in energy management contributes to the development of severe obesity and is exacerbated by factors limiting physical activity such as marked daytime sleepiness, disturbances of circadian rhythms, and neurological deficits [160]. The degree of obesity frequently increases early after treatment and rapid weight gain frequently occurs during the first 6 to 12 month after treatment [142, 155, 157] . Following treatment, the prevalence of severe obesity is higher, reaching up to 55% [24, 140-142, 150, 155, 161-163]. Obesity and eating disorders result in increased risks of metabolic syndrome [150] and cardiovascular disease [158], including sudden death events [164], increased multisystem morbidity [144], and increased mortality [77, 140, 165-171].
Although the relation of severe obesity with hypothalamic lesions is obvious in craniopharyngioma patients [157, 158, 172], the mechanisms responsible for increased prevalence of cardiometabolic complications in these patients are still unclear. It is likely that in cases of suprasellar extension, hypothalamic function will be compromised and will remain compromised to a certain extent when treated surgically or with irradiation. Although it is a relatively small structure of only 4 ml volume, the

hypothalamus contains several groups of nerve cell bodies forming distinct nuclei, which have highly diverse molecular, functional, and structural organization [173]. The hypothalamus plays a predominant role in keeping the internal environment stable by synchronizing biological clock mechanisms and circadian rhythms. Recent data indicate that an adequate balance of the autonomic nervous system equilibrium is crucial for metabolism. It is well known that adipose tissue is richly innervated by sympathetic nerve fibers that control lipolysis. Consequently, it appears that lipogenesis is also controlled by parasympathetic innervation of adipose tissue originating from separate sympathetic and parasympathetic neurons in the periventricular nucleus and suprachiasmatic nucleus [174]. Such a high level of differentiation puts the suprachiasmatic nucleus in a key position to balance circadian activity of both branches of the autonomous nervous system. Considering the large proportion of craniopharyngioma patients with damage to suprasellar structures, it is likely that craniopharyngiomas involving hypothalamic areas and/or the effects of treatment of these tumors compromise the functionality of the suprachiasmatic hypothalamic nucleus. This affects the regulation of central clock mechanisms, which predisposes to alterations in metabolism. Clearly, surgical strategies to preserve hypothalamic integrity are mandatory for the prevention of sequelae such as severe obesity owing to hypothalamic lesions.
When elevated serum leptin levels relative to BMI were found in childhood craniopharyngioma patients with a suprasellar tumor extension [175], researchers suggested that normal appetite inhibition failed to occur in these patients due to disruption of hypothalamic receptors that regulate the negative feedback loop in which leptin, formed in adipocytes, binds to hypothalamic leptin receptors. However, a study involving self-assessment by nutritional diaries revealed that hypothalamic obesity also occurs in patients with childhood craniopharyngioma even when caloric intake is comparable to controls matched for BMI [176].

2.11.1.5. Physical activity and energy expenditure

An analysis of physical activity by accelerometric assessments showed that childhood craniopharyngioma patients had a markedly lower level of physical activity than healthy controls matched for BMI [176]. Concomitant visual and/or neurological compromise should also be taken into account for the observed reduction of physical activity in craniopharyngioma patients. Additionally, markedly increased daytime sleepiness and disturbances of circadian rhythms have been demonstrated in patients with childhood craniopharyngioma and severe obesity [160]. Daytime sleepiness and obesity in these patients were both correlated with low nocturnal and early morning melatonin concentrations in saliva. The suspected pathogenic mechanism in patients with childhood craniopharyngioma involves impaired hypothalamic regulation of circadian melatonin secretion. Initial experiences with oral melatonin substitution in childhood craniopharyngioma patients (6 mg melatonin per day) were promising: melatonin levels normalized and physical activity and daytime sleepiness improved significantly [177]. However, data on the long-term effect of melatonin substitution on weight development and daytime sleepiness have not yet been published.
Polysomnographic studies in patients with childhood craniopharyngioma and severe daytime sleepiness have revealed sleep patterns typical for hypersomnia and secondary narcolepsy, i.e., frequent sleep-onset REM phases (SOREM) [161, 178, 179]. Medication with central stimulating agents (methylphenidate, modafinil) had a markedly beneficial effect on daytime sleepiness in these patients [178]. Regarding disturbances of circadian rhythm, secondary narcolepsy should be taken into consideration as a pathogenic factor in severely obese childhood craniopharyngioma patients. Mason *et al.* [180] treated five patients with childhood craniopharyngioma and severe hypothalamic obesity (age range: 6.0 to 9.8 yrs) with the central stimulating agent dextroamphetamine for the purpose of weight reduction. Dextroamphetamine therapy stabilized patients' BMI and the patients' parents reported marked improvements in their child's physical activity and alertness.
A decreased metabolic rate, in terms of both increased resting and decreased total energy expenditure, has been suggested to contribute to weight gain in patients with childhood craniopharyngioma. Adults and pediatric patients with childhood-onset craniopharyngioma were found to have a lower resting–energy expenditure (REE) compared to controls [157, 181, 182] that could not be explained by differences in terms of body composition. This energy intake / REE ratio was lower in those with tumors involving the 3rd ventricle [157]. Impaired physical activity is also likely to contribute to an overall lowering of total energy expenditure [157, 158, 176, 181]. Further factors potentially contributing to decreased physical activity are neurological and visual deficits, psychosocial difficulties, and increased daytime sleepiness.

2.11.1.6. Autonomous nervous system

Lustig and colleagues [183, 184] hypothesized that hypothalamic disinhibition of vagal output is a cause of increased β-cell stimulation in patients with childhood craniopharyngioma, and that this disinhibition leads to hyperinsulinism and severe obesity. They therefore studied treatment with the somatostatin analogue octreotide, which suppresses β-cell activity [183].
Several reports [185, 186] hypothesized that decreased physical activity and severe obesity in patients with childhood craniopharyngioma are likely related to impaired central sympathetic output. For instance, Roth *et al*. observed reduced urine concentrations of catecholamine metabolites correlating with the degree of obesity and the level of physical activity [187].

2.11.1.7. Appetite regulation

Roth and colleagues recently analyzed the gastrointestinal hormones ghrelin and peptide YY and brain-derived neurotrophic factor and their effect on satiety regulation in patients with childhood craniopharyngioma and hypothalamic obesity [188, 189]. Their findings support the hypothesis that reduced ghrelin secretion and impaired postprandial suppression of ghrelin in patients with childhood craniopharyngioma and severe hypothalamic obesity leads to disturbed regulation of appetite and satiety. Peptide YY serum concentrations did not differ between normal weight, obese, and severely obese patients with childhood craniopharyngioma. A possible pathogenic role of peripheral α-melanocyte-stimulating hormone in childhood craniopharyngioma obesity has also been reported [190].
Hoffmann *et al.* [191] analysed eating disorders and eating behaviour in 101 survivors of childhood-onset craniopharyngioma and 85 BMI-matched healthy controls. Severely obese patients (BMI >+8 SD; n=9) presented with pathological eating behaviours and more weight problems and eating disorders, as compared to obese (BMI +3 to +8 SD; n=44) and normal or overweight patients (BMI <+3 SD; n=48). However, childhood-onset craniopharyngioma patients with different degree of obesity showed similar or even less pathological findings as compared to BMI-matched normal controls. Hoffmann *et al.* conclude that the observed eating disorders are not disease-specific for childhood-onset craniopharyngioma.
Roth *et al.* [192] assessed pre- and post-meal responses to visual food cues in childhood-onset adamantinomatous craniopharyngioma patients' brain regions of interest using functional magnetic resonance imaging (fMRI). Following a test meal, BMI-matched controls showed suppression of activation by high-calorie food cues while childhood-onset craniopharyngioma patients showed trends toward higher activation. These findings support the hypothesis that perception of food cues especially after food intake may be altered in childhood-onset craniopharyngioma patients with hypothalamic obesity.
Even though hypothalamic obesity is a frequent sequela in childhood-onset adamantinomatous craniopharyngioma [188], also diencephalic syndrome leading to severe weight loss and cachexia can occur as a rare hypothalamic disturbance of body composition in childhood-onset craniopharyngioma [193, 194]. Hoffmann *et al.* [194] analysed the incidence of diencephalic syndrome, its clinical manifestations before and after diagnosis of childhood-onset craniopharyngioma, and outcome in 485 patients recruited in the German childhood craniopharyngioma registry. Only 4.3% of all childhood-onset craniopharyngioma patients presented with low weight (BMI <-2 SD) at time of diagnosis. Initial significant differences between patients with low weight at the time of diagnosis and normal weight patients at diagnosis are usually observed at 5 yrs of age. Within the first two yrs after diagnosis of childhood-onset craniopharyngioma, the BMI of diencephalic syndrome patients and normal weight patients converge to a similar level. Hoffmann *et al.* concluded from their analysis of patients' histories that diencephalic syndrome at the time of diagnosis does not preclude subsequent weight gain caused by a childhood-onset craniopharyngioma with hypothalamic involvement.

2.11.1.8. Pharmacological treatment of hypothalamic obesity

Due to disturbances in energy expenditure, central sympathetic output, and appetite-regulation, craniopharyngioma patients with hypothalamic obesity typically develop morbid obesity that is mainly unresponsive to conventional lifestyle modifications (diet and exercise) for regulating BMI. Based on impairment of sympathoadrenal activation and epinephrine production manifesting as a reduced hormonal response to hypoglycemia, treating this disorder with amphetamine derivatives has been suggested [195, 196]. Use of dextroamphetamine intervention starting 10 month post-surgical and lasting 24 month was shown to diminish continuous weight gain and to stabilize BMI [180]; importantly, spontaneous physical activity increased significantly. Even shorter periods of dextroamphetamine treatment have caused a subjective improvement in daytime sleepiness [197]. Also, Elfers *et al.*

observed beneficial effects of central stimulating agents (particularly methylphenidate) on weight development in craniopharyngioma patients [198].
Craniopharyngioma patients with hypothalamic obesity have a so-called parasympathetic predominance of the autonomic nervous system induced by vagal activation, manifesting as daytime sleepiness, reduced body temperature and lowering of heart rate [199]. Parasympathetic stimulation causes insulin secretion by way of direct activation of β-cells as well as promoting adipogenesis. As insulin is an anabolic hormone, it has been suggested to be an important driver of weight gain in hypothalamic obesity. Octreotide is a somatostatin analogue and thus causes reduction in insulin secretion. Lustig and colleagues used octreotide in a double blind randomized controlled study in children with hypothalamic obesity and demonstrated moderate reductions in weight gain [183]. The authors showed that insulin levels during a proof-of-concept oral glucose tolerance test decreased without leading to major changes in glucose tolerance. This study was followed by a larger trial performed using octreotide LAR (long-acting repeatable) in 60 patients with cranial surgical interventions that led to hypothalamic obesity [200]. This 6- month intervention showed no efficacy in changing BMI and the open label segment of this study was terminated earlier than planned due to an increased risk of gallstone formation.
Zoicas *et al.* [201] treated 8 adult patients (6 craniopharyngioma) with hypothalamic obesity with GLP-1 analogues and observed a substantial and sustained weight loss associated with improvements in metabolic and cardiovascular risk profiles.
Daubenbüchel *et al.* [202] recently reported that craniopharyngioma patients are able to produce and secrete the hormone oxytocin, even when pituitary and hypothalamic structures were damaged. However, patients with hypothalamic damage grade 1, which involves damage only to the anterior hypothalamic areas, presented with a lower fasting level of oxytocin. In addition, changes in oxytocin levels before and after standardized breakfast correlated with BMI, demonstrating that craniopharyngioma patients with hypothalamic obesity show less variation in oxytocin secretion due to nutrition. Accordingly, the authors speculate that oxytocin supplementation might be a therapeutic option in craniopharyngioma patients with hypothalamic obesity and/or neurobehavioral deficits due to specific hypothalamic damage in the anterior hypothalamic area. Hoffmann *et al.* reported on first preliminary results of a small pilot study testing this hypothesis by single nasal oxytocin application in 11 craniopharyngioma patients [203]. All patients presented with detectable levels of oxytocin before administration. Nasal administration of oxytocin was well tolerated and resulted in increased oxytocin concentrations in saliva and urine. After oxytocin administration, craniopharyngioma patients with postsurgical lesions limited to the anterior hypothalamus area showed improvements in emotional identifications compared to craniopharyngioma patients with lesions of anterior and posterior hypothalamic areas. Focusing on correct assignments to positive and negative emotion categories, craniopharyngioma patients improved assignment to negative emotions.
Up to now, there are only rare case reports on long-term effects of oxytocin treatment in craniopharyngioma reporting on parent-observed neuro-behavioral and pro-social improvements after 22 month of treatment [204] and in a second case on weight loss and reduced hyperphagia due to oxytocin therapy (10 weeks) followed by combined therapy with oxytocin and naltraxone treatment over a 38 weeks period [204].
A multicenter clinical trial titled „Intranasal Oxytocin to Promote Weight Loss in Children, Adolescents, and Adults With Brain Tumors and Hypothalamic Obesity Syndrome“ (ClinicalTrials.gov Identifier: NCT 02849743 [205]) is currently recruiting patients for randomized testing if oxytocin, delivered by nasal spray, will promote weight loss in children, adolescents, and adults with hypothalamic obesity as compared to a placebo.

2.11.1.9. Bariatric treatment of hypothalamic obesity

Initial experiences with bariatric surgery in severely obese childhood craniopharyngioma patients achieved sufficient tolerability and short-term weight reduction [206-208]. An instant improvement of binge-eating behavior in patients with childhood craniopharyngioma immediately after laparoscopic adjustable gastric banding (LAGB) was observed, but failed in long-term weight reduction. Nevertheless, obesity prevention intervention could be achieved during regular follow-up monitoring [209].
In a systematic review and meta-analysis of the literature, Bretault *et al.* [210] analyzed the 12- month outcome after bariatric surgery for hypothalamic obesity due to craniopharyngioma treatment. At one yr, 6 of 18 cases with follow-up data had lost more than 20% of their initial weight; all had undergone either Roux Y gastric bypass (n=3), sleeve gastrectomy, (n=2) or biliopancreatic diversion (n=1). All patients who had lost less than 5% of their initial weight had undergone LAGB, except one Roux Y gastric bypass case. These findings indicate that Roux Y gastric bypass, sleeve gastrectomy, and biliopancreatic diversion are the most efficient bariatric procedures for weight reduction in hypothalamic obesity of

childhood craniopharyngioma patients. However, treatment with invasive, non-reversible bariatric methods is controversial in the pediatric population because of medical, ethical, and legal considerations [209, 211, 212].
Despite the availability of the above-mentioned promising therapeutic approaches, it must be emphasized that in the studies published to date no generally accepted (pharmacological or bariatric) therapy for hypothalamic obesity in childhood craniopharyngioma has been shown to be effective in randomized studies [213].

2.11.1.10. Quality of life, neurocognitive outcome and psychosocial functioning

QoL in craniopharyngioma patients can be affected by both the tumor itself and the treatment received. Reports assessing psychosocial and physical functioning show variable results, ranging from excellent in a majority of subjects to impaired function in almost half of the patients [24, 140, 214-217]. The most common areas of difficulty reported include social and emotional functioning, with patients rating their psychosocial status to be lower than their physical health [140]. Other reported challenges included somatic complaints such as reduced mobility, pain, and self-care [52, 140]. Behavioral questionnaires indicate a high rate of psychopathological symptoms, including depression, withdrawal, and anxiety. The most frequent problems in children's everyday functioning include difficulties in learning, inability to control emotions, unsatisfactory peer relationships, and concerns regarding physical appearance and body image [148, 218].
Reported factors associated with worsening quality of survival outcomes as well as neurocognitive and psychosocial functioning include younger age at diagnosis and preoperative functional impairment. Furthermore, tumor characteristics - including larger tumor volume, hypothalamic and 3rd ventricle involvement at presentation - are reported in the literature to complicate both pre- and post-surgical conditions and therefore survival and QoL outcomes in these patients [33, 40, 139, 219]. Treatment strategies have also been implicated with worse outcomes for surgery alone compared to limited surgery followed by irradiation and for multiple operations for tumor recurrence. Endocrine, neurological, and ophthalmological sequelae all adversely affect QoL outcome [24, 52, 136, 137, 140, 214, 215]. Hypothalamic dysfunction has been found to have the most important negative impact on social functioning, physical ability, and body image [140, 155, 215].
Long-term neurocognitive complications following treatment for craniopharyngioma include cognitive problems, particularly those affecting executive function, attention, episodic memory and working memory [140, 148, 218, 220-225]. Özyurt *et al.* [226] observed that childhood craniopharyngioma patients had lower performance scores in tests of memory and executive functioning when compared with normal controls. Performance in executive functions and functional capabilities were negatively associated with the degree of hypothalamic involvement and damage.
Long-term survivors of childhood craniopharyngioma treated primarily with subtotal surgical resection followed by irradiation were also found to have psychological and educational deficits [148]. Neurocognitive deficits include memory disturbances, slower cognitive speed, attention problems, and behavioral instability [148, 218, 220, 222, 223, 227]. While intact intellectual functioning has been reported in up to 82% of patients, visual memory is impaired despite normal visual-spatial abilities [148, 218]. The acquired deficits in higher cognitive processing such as attention problems are considered precursors to poor academic achievement.
Despite over a quarter of century of literature documenting the neurocognitive challenges encountered by individuals treated for craniopharyngioma, intervention efforts have lagged. Recent case studies have examined the efficacy of cognitive rehabilitation for dysexecutive problems and behavioral lability [228, 229]. Taken together, these case studies suggest that cognitive rehabilitation approaches such as goal management therapy and functional behavioral analysis appear to be useful diagnostic and therapeutic options, compensating for cognitive and psychosocial challenges [230].

2.11.1.11. Cerebrovascular morbidity

Radiation-induced vasculopathies are a rare consequence of radiation therapy for craniopharyngioma. In patients irradiated for craniopharyngioma, moyamoya syndrome (a radiation induced cerebrovascular condition predisposing to stroke) has been described [50, 231]. A retrospective estimate was that 27% of 22 patients treated with irradiation and some combination of surgery and intracystic chemotherapy with a median radiation dose of 52.2 Gy developed some type of vasculopathy, only half of which were symptomatic [231]. Although in this study no association was found between age, radiation dose and maximum or mean dose to the internal carotid arteries with the presence of vascular abnormalities, Regine and colleagues reported a 13.7% rate of cerebrovascular events, all in irradiated cases receiving over 61 Gy [232]. No cerebrovascular clinical events have been reported in any other series of conventionally fractionated radiotherapy for craniopharyngioma, including those with large patient

numbers [48, 51, 69, 82, 83, 233, 234]. Fusiform dilatation of the carotid artery on postoperative magnetic resonance imaging has been noted in 10–29% of children after radical surgery. The natural history appears to be benign, and there have been no anecdotal or published reports of hemorrhage or stroke attributable to these lesions to date [235-237].

2.11.1.12. Second malignant neoplasms

In the largest reported series, no second malignancies in the irradiated field were observed in 173 irradiated patients with a median follow-up of 12 yrs [51]. Three long-term survivors (2%) died of systemic malignancies with unspecified diagnoses. Overall, only four cases of second malignancies have been reported [50, 78, 88, 238], comprising 2 in-field glioblastomas [78, 238], one in-field glioma with unspecified grade of malignancy [50] and a posterior fossa meningioma [88].

2.11.1.13. Survival and late mortality

Craniopharyngiomas are associated with significant mortality, with reported overall mortality rates three to five times higher than those of the general population [144, 239]. When assessing mortality in patients with craniopharyngioma, the literature indicates that it is important to consider cases in adult- and childhood-onset craniopharyngioma separately. The overall survival rates (which reflect the effect of multiple treatments) described in exclusive children series range from 83–96% at 5-yr [23, 43, 78, 155, 166, 167, 238] and 65–100% at 10-yr [23, 78] [24, 50, 139, 140, 165, 166, 168-171, 238, 240] and average 62% at 20-yr [232]. In adults or a mixed-age range population (adults and children) series, the overall survival rates range from 54–96% at 5-yr [20, 38, 48, 51, 82, 144, 214, 233, 238, 241], from 40–93% at 10-yr [38, 48, 51, 82, 136, 144, 214, 233, 238, 239, 241], and from 66–85% at 20-yr [51, 82, 144] (Table 7). The lower limits of survival rates usually reflected data from earlier series, before modern advances in microsurgery, neuroimaging, and radiotherapy. It is not clear whether the age at diagnosis represents a survival prognostic factor because some studies have shown that the youngest patients have better survival rates [20, 38, 238, 239]; others have found better outcome in older patients [51, 219], whereas still other studies report no difference between pediatric and adult populations [48, 82, 233, 242, 243]. The role of gender as a prognostic factor is not established; some authors report a higher mortality among females [144, 239], but others have not found any gender differences [48, 166, 233, 243]. One of the two studies reporting higher mortality rates in females suggested a possible role of estrogen deficiency [144], but the other study did not consider that unsupplemented gonadal insufficiency had a significant impact on enhanced mortality [239].

Disease related mortality can occur even many yrs after treatment. Causes of late mortality include those directly related to the tumor or its treatment such as progressive disease with multiple recurrences, chronic hypothalamic insufficiency, hormonal deficiencies, cerebrovascular disease and seizures [136, 137, 139, 140, 165]. Other causes have been described, including decreased mineral bone density and non-alcoholic steatohepatitis, leading to liver cirrhosis in some cases [22, 140, 162, 165, 244-248]. A recent review has reported substantial long-term morbidity with hypopituitarism, increased cardiovascular risk, hypothalamic damage, visual and neurological deficits, reduced bone health, and reduction in QoL and cognitive function. The standardized overall mortality rate varies from 2.88 to 9.28 in cohort studies covered in this review. According to the review, craniopharyngioma patients have a 3- to 19-fold higher cardiovascular mortality in comparison to the general population, and female craniopharyngioma patients have an even higher risk [143].

Tumor size is likely to be a prognostic factor because increased survival rates have been shown in tumors with a diameter smaller than 3 cm [242]. The histological type as a prognostic factor is also controversial; better 5-yr survival rates have been found in the squamous epithelial type vs. the adamantinomatous and combined histological types [249]. Higher perioperative deaths have also been reported in adult adamantinomatous tumors [250], but other authors have not found significant differences between the two histological types [251, 252]. Several studies have described a more favorable prognosis when tumors lack calcification, especially in adult craniopharyngioma patients [242, 250], although no specific pathological feature predicted survival in childhood craniopharyngioma patients [167]. In other studies, neither tumor histology [48, 242] nor tumor location [48, 166] had prognostic importance. In childhood craniopharyngioma patients, the use of modern imaging as well as a good initial performance status (measured according to a functional classification that includes the presence of hypopituitarism, visual deficits, and neurological impairment) have been correlated with enhanced overall post-surgical survival at 10-yr [78]. It is not clear whether the presence of hydrocephalus constitutes a prognostic factor because increased mortality [219] and lack of association with mortality have been reported [48, 166, 167, 233, 253].

Sterkenburg *et al.* [254] recently reported that hypothalamic involvement had a significant negative impact on 20-yr overall survival. The degree of surgical resection had no effect on 20-yr progression

free survival rate in craniopharyngioma survivors, supporting the concept that gross-total resection was of no advantage in terms of tumor recurrence.

2.11.1.14. Neuropsychological deficiencies

Animal studies have demonstrated that electrical stimulation of the amygdala, septal nuclei and posterior hypothalamus causes aggression attacks and intermittent, explosive behavior [255]. Cat models showed that electrical stimulation of the posterior lateral hypothalamus can lead to hyperphagia in addition to the above mentioned aggressive behavior attacks. It turned out that several cases where the ventromedial nucleus was affected resulted in both hyperphagia and disinhibited aggressive behavior [256, 257].

In humans, hypothalamic lesions can bring about emotional lability, fury attacks, abnormal sexual behavior, and deficits in memory and intellectual capacities [258]. Flynn *et al.* [256] reports a *neurobehavioral syndrome* with the four main symptoms: (1) episodic tantrums, (2) emotional instability, (3) hyperphagia with attendant obesity, and (4) intellectual impairment. According to Flynn, this syndrome is especially germane 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 behavior 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 [259]. Children with tumors of the third ventricle display symptoms of amnesia, confusion and consciousness impairment [260]. Lesions of the ventromedial prefrontal cortex whose victims display symptoms of poor impulse control and attention deficits have also been documented [261].

Tonkonogy *et al.* [262] attribute the posterior hypothalamus and its relationship to components of the limbic system as having significant importance as it is from there that socialized inhibition of aggressive behavior occurs. In the opinion of these authors, aggressive behavior 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 [263]. 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 key to planning surgical strategies (gross total resection vs. partial resection plus immediate irradiation) with regard to long-term QoL effects.

The predominant indicator found in the literature is postoperative normal intelligence quotients (IQ) for adult craniopharyngioma patients [24, 264], yet only anecdotal reports have been published on diminished postoperative intelligence results [265, 266]. Honegger and colleagues prospectively studied a small collective (n=13) of adult craniopharyngioma patients following mostly transsphenoidal resections and found no impairments regarding their neuropsychological status [267]. However, several studies of children with craniopharyngioma yielded disturbances of memory, attention, impulse control, motivation and socialization [268-273]. The correlation between cognitive interferences and radical resection remains controversial [271, 274]. It is generally agreed that neuropsychological consequences following irradiation are dependent upon the child's age, irradiation volume, individual dosages, fractionated method 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 [275]. As of yet there are no published prospective investigations regarding neuropsychological prognoses of children and adolescents with craniopharyngioma.

In a first review on cognitive performance in patients with childhood-onset craniopharyngmioma, we recently summarized and systemized findings obtained with formalized neuropsychological testing [225]. Notably, detailed neuroradiological assessment of the tumor or lesion site with respect to the hypothalamus was only performed in few of the studies [226, 276, 277]. A systematic assignment of test results to subcomponents of cognition contributed to a comprehensive picture of spared and impaired cognitive functions associated with craniopharyngiomas or their removal. With few exceptions [278, 279], IQ scores were shown to be in the normal range [24, 226, 263, 264, 276, 280-283], albeit Bawden [281] found significantly lower IQ scores when compared to a healthy control group. Despite well-preserved overall cognitive abilities, several studies obtained significant deficits in tests assessing memory, attention, processing speed, and executive functioning.

In accordance with frequent complaints of children and their caregivers [284], memory is the most investigated cognitive domain in childhood-onset craniopharyngioma. Typically, deficits were shown for episodic memory, which is a consciously accessible memory system that allows to re-experience past events or episodes in life including their spatial and temporal context [285]. Tests used to assess episodic memory most frequently include list-learning tasks, story memory tasks or complex geometric designs [286]. In several studies, encoding in long-term memory and/or episodic long-term retention were shown to be impaired, including verbal as well as visual/visuo-spatial information [226, 276, 277, 282], [but see 287, 288]. Waber *et al.* [280] reported on severe impairments in a narrative task (story memory) but not in a word list or visual memory task. In one of the studies [277], additional analyses indicated that patients with hypothalamic involvement were mainly responsible for the deficits reported for the whole patient group. Noteworthy, in the two studies that tested delayed recognition memory, performance was found to be preserved, despite findings of deficient episodic memory recall [226, 276]. Where tested, verbal and visuo-spatial short-term memory were also found to be in the normal range [263, 276, 280] or not different from controls [226].
Only few studies tested executive functions with formalized questionnaires or tests. In a study that used a standardized questionnaire to assess everyday problems with executive functions, Laffond *et al.* [93] reported a high proportion of children to suffer from deficits. In studies using neuropsychological testing, cognitive flexibility, which is of vital importance for the ability to adapt to changing situations and goals, was often shown to be impaired [226, 263, 272]. However, Bawden *et al.* [281] did not find any deficits in tasks assessing executive performance (cognitive flexibility, verbal and figural fluency and concept formation). Results on sustained attention are inconsistent, with findings of both, impaired [226, 277] and unimpaired performance [280, 288]. Studies that tested cognitive processing speed found abnormal slow performance in the patient groups [277, 280]. The inconsistent results, for attentional control in particular, may be partly due to the small and heterogeneous patient samples in the currently available studies on cognitive performance in childhood-onset craniopharyngioma.

2.11.1.15. Social-emotional performance

Aside from cognitive deficits, craniopharyngioma patients often suffer from emotional dysregulations and social impairments, severely affecting health-related QoL. Those impairments significantly challenge families, friends, and the patients' ability to perform in school and working environments [140, 282, 289]. Frequently reported abnormalities include depression, anxiety, mood swings, emotional outburst and irritability in the emotional domain, and hostility and aggressiveness in the social domain. In a systematic literature review, emotional dysfunctions were reported for 40% of the childhood-onset craniopharyngioma patients. Social withdrawal was reported for 35% of the patients [290]. The relevance of acquiring both, self- and other-reports, is nicely illustrated in a study by Poretti et al. [140]. By using the Child Behavior Checklist (CBCL) and the Youth Self Report (YSR) [291], they found that 33% of the pediatric patients reported social problems in their everyday interactions. Interestingly, parents' ratings of children's social problems were much higher (58%), a discrepancy which they also reported for other dimensions, such as externalizing behavior. It should be noted, however, that studies on social-emotional functioning are all based on questionnaires. Hence, objective data based on experimental tasks or neuropsychological testing are not available yet.
Disease-related changes such as severe obesity and loss of functional abilities may trigger significant social-emotional reactions, including anxiety, depression, and social withdrawal. At the same time, neuropathological changes in the hypothalamus and associated limbic networks clearly increase the likelihood of adverse outcomes in mood and behavior [292]. However, most of the studies investigating social-emotional abnormalities in craniopharyngioma patients did not report tumor or lesion location with respect to the hypothalamus and some of them not even considered the relevance of these factors [e.g., 280, 282]. This is remarkable, as some of the patients' deficits are similar to or at least reminiscent of abnormalities reported for hypothalamic lesions in single-case studies of humans, and in animals [293, 294]. In studies, which explicitly considered the role of the hypothalamus for neurobehavioral performance, deficits in emotion and interpersonal relationships were shown to be worse in patients with hypothalamic involvement, compared to those without hypothalamic involvement [93, 140, 289]. A further shortcoming of the current literature is the virtual lack of a detailed assessment of specific social and emotional domains. Almost all studies in the field used QoL questionnaires and the Child Behavior Checklist, which both provide a first valuable assessment, but are not suitable for providing detailed information on specific subdomains of social-emotional functions. Moreover, several functional domains, which may be impaired due to the location of the tumor and potential damage in associated limbic networks, have not been considered yet (e.g., emotion regulation strategies and social cognition).

2.11.1.16. 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 [295]. However, as of yet there is no published report on prospective, multicenter study results (self-rated / parents-rated) for health-related craniopharyngioma patient QoL.

In the HIT-ENDO cross-sectional study, 185 children and adolescents were assessed no less than two yrs after their craniopharyngioma diagnosis by means of questionnaires (KINDL, PedQol, EORTC-QIQ-30) regarding their QoL. The QoL data were evaluated in reference to grade of resection, irradiation, and BMI (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 longterm. It can be concluded from these interim results that craniopharyngioma affects the QoL of children and adolescents with this disease 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 prospective QoL and life situation monitoring is organized for children and adolescents with brain tumors (HIT-Leben; project manager: Dr. G. Calaminus, Bonn). A goal of the HIT-Leben 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 integratable questions referencing, for instance, effects of individual tumor entities, or potential cofounding variables such as patient age and gender. KRANIOPHARYNGEOM 2007 data assessment was carried out using standard HIT-Leben guidelines in alignment with the above-mentioned goals.

2.11.1.17. Brain abnormalities in childhood-onset craniopharyngioma

Craniopharyngiomas bear a significant risk for the integrity of fronto-limbic networks, even beyond the damage directly resulting from tumor growth. First, as in other brain tumors, a number of treatment-related factors, such as surgical approaches, radiation therapy, and complications may worsen tumor-related damage and may also result in damage to other areas [296]. Second, hypothalamic lesions may trigger proximal and distal changes in connected brain areas (through diaschisis or transneuronal degeneration), which then add to impairments in cognitive, social and emotional performance often observable in patients [297]. Such secondary processes are likely to be spread along hypothalamic connections with fronto-limbic subsystems: a posterior subsystem that constitutes a neural system supporting episodic memory and an anterior subsystem supporting emotional, motivational and social functioning [298, 299]. Notably, the neurobehavioral deficits most frequently reported for craniopharyngioma patients strikingly correspond to the functional range of these two subsystems.

Brain abnormalities associated with craniopharyngioma surgery have only been investigated recently. In a PET-study with childhood-onset craniopharyngioma patients, several tumor- and treatment-related

metabolic abnormalities were found after surgery and before proton therapy. A hypometabolism was observed in parts of the frontal lobe, medial/inferior temporal lobe, limbic areas, caudate nucleus, and cingulate gyrus, together with a hypermetabolism in parts of the contralateral temporal and parietal lobes [296]. Main predictors for the hypometabolism were hydrocephalus, sex and the number of surgical interventions. Interestingly, the authors also reported results of a patient with transsphenoidal surgery only, i.e. without operative trauma to limbic or frontal areas. For this patient, hypometabolism was observed in fronto-limbic areas, indicating the potential consequences of hypothalamic lesions for the integrity of connected brain areas. This result is well in line with findings of an fMRI study from our lab, which focused on childhood-onset craniopharyngioma patients with hypothalamic involvement and was the first to provide evidence for distal effects of hypothalamic injury in humans [226]. As patients in our study were highly selected due to our exclusion criteria, they had a very low rate of complications and additional surgeries compared to those in the PET-study. Nevertheless, when compared to age- and intelligence-matched healthy controls, patients with hypothalamic involvement had a failure of task-related deactivation in orbital and adjacent medial frontal cortex during memory recognition. This failure of deactivation was assumed to be functionally related to the altered functional coupling which we observed between patients' rostral medial prefrontal cortex and the thalamus [300]. Findings of these two imaging studies, together with preliminary findings of a study on social cognition from our lab (unpublished; see section Preliminary Results), motivated a retrospective analysis with voxel-based morphometry (VBM) to investigate whether hypothalamic lesions also impact on brain structure in areas strongly connected to the hypothalamus. In line with our hypothesis, patients compared to healthy controls revealed significantly reduced grey and white matter volumes in anterior and posterior limbic networks. Within the patient group, worse long-term memory retrieval was correlated with smaller grey matter volumes in the posterior cingulate cortex. The volumetric differences between patients and controls were also observed when lesions caused by surgical pathways and complications were accounted for as far as possible. Thus, our data provided the first evidence for grey and white matter volume reductions outside the area of tumor growth in patients with childhood-onset craniopharyngioma and hypothalamic involvement.

3. Concepts of KRANIOPHARYNGEOM Registry 2019 as a project following the trials HIT-ENDO and KRANIOPHARYNGEOM 2000/2007

3.1. Background

HIT-ENDO and KRANIOPHARYNGEOM 2000/2007

Based on the KRANIOPHARYNGEOM 2000/2007 results as well as published results of collaborative studies in connection with HIT-ENDO and KRANIOPHARYNGEOM 2000/2007, the following conclusions can be made:

- Hypothalamic involvement resulting in radical surgical procedures and hypothalamic lesions are both clear predictors for impairments in postoperative functional capacities and QoL [33, 64].
- Considering the long-term consequences in cases of craniopharyngiomas with hypothalamic involvement, it appears that intended radical neurosurgery is **not** advisable [301].
- Patient QoL is seriously impaired in ca. 50% of craniopharyngioma cases due to damage-induced hypothalamic obesity [40, 302].
- Patients with severe obesity presented reduced long-term functional capacities following multiple neurosurgical interventions in the course of treating the disease [215, 217].
- The most significant increase in BMI in patients at risk for obesity occurs during the first 12 month after diagnosis/surgery [155].

Patients with hypothalamic involvement should be classified as high risk regarding long-term consequences and impaired long-term prognosis based on the results of the above-mentioned analyses. There is consensus that complete resections are to be avoided for hypothalamic involved tumors based on the known, long-term consequences.

3.2. Aims of KRANIOPHARYNGEOM Registry 2019

3.2.1. Data collection on diagnostics, history before diagnosis, pathological and molecular findings, treatment modalities (neurosurgery, irradiation, intracystic therapy), endocrine status before and after treatment, morbidities, neuropsychological findings and quality of survival (QoS) during follow-up after primary diagnosis of childhood-onset craniopharyngioma.

3.2.2. Reference-assessment of pathological findings, imaging results (pre and post OP), surgical approaches and strategies, planning and performance of irradiation,

3.3. Work program

3.3.1. Patient recruitment: All patients, which are newly diagnosed with childhood-onset cranio-pharyngioma (age at diagnosis ≤18 yrs) and registered by specialists involved in their treatment and follow-up care, will be informed about the procedures and aims of the registry. Additionally, patients with xanthogranuloma, cysts of Rathke's pouch, meningioma, pituitary adenoma, and arachnoid cysts will be enrolled in the registry.

The application form for registering patients in the German Childhood Cancer Registry (DKKR) is available in all centers. It is the same form for all tumors and after completion it 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. 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 (Dr. C. Ronckers, IMBEI at University Mainz).

3.3.2. Interventions: Interventions are not part of the project.

3.3.3. Data acquisition: see CRFs (Appendix section16).

4. Statistical methods and design of KRANIOPHARYNGEOM Registry 2019

4.1. Patient recruitment and admission

All patients meeting the inclusion and no exclusion criteria will be enrolled in the KRANIOPHARYNGEOM Registry 2019.

Inclusion criteria:

- Confirmed histological diagnosis of craniopharyngioma in patients ≤18 yrs by reference pathology
- Informed consent by legal guardians and/or patient to contribute data to the registry

Additionally, Patients with pituitary adenoma or meningioma will be reported by the German Pediatric Cancer Registry (DKKR) to the study coordinator in Oldenburg. Data regarding frequency, diagnostic features, treatment and follow-up in these patients will be collected in context of KRANIOPHARYNGEOM 2019 (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 2019. Patient whose imaging indicated a suspected craniopharyngioma, but histological analysis revealed a different diagnosis will be referred, along with their corresponding pathological findings, to the respective GPOH study responsible for these entities.

Exclusion criteria:

- Absence of informed consent by legal guardians and/or patient to contribute data to the registry

4.2. Statistical endpoints and independent variables

The present protocol is a prospective, multicenter registry with the goal to observe and analyse multidisciplinary treatment approaches in childhood-onset craniopharyngioma. Therefore, several endpoints were chosen that reflect patients' survival and QoL. The association between these endpoints and a set of independent variables that represent diagnostic characteristics and treatment strategies will be analysed. On the basis of previous analyses (e.g., KRANIOPHARYNGEOM 2000 / KRANIOPHARYNGEOM 2007), the independent variables have been divided into two categories according to their expected influence on outcome and prognosis of childhood-onset craniopharyngioma.

Endpoints:

- Overall survival (OS) defined as time from diagnosis to death
- Progression-free survival (PFS) defined as time from diagnosis to progression or death (whichever occurs first)
- Quality of life (PedQol, PedsQL, FMH)
- Degree of obesity (BMI SDS)

Factors of influence (mandatory):

- Tumor location (grade of hypothalamic involvement, grade 0-2)
- Neurosurgical treatment strategy (intended radical resection vs. incomplete resection + XRT)
- Realized degree of surgical resection (complete resection vs. incomplete resection)
- Postsurgical hypothalamic lesions (grade 0-2)
- Irradiation: modality (photon vs. proton beam therapy) and treatment (dose)

Factors of influence (potential):

- Clinical manifestations and symptoms in history
- Duration of history
- Histology (adamantinomatous vs. papillary type)
- Hydrocephalus at diagnosis
- Patient load of treating neurosurgical units (based on patient load during 10 yrs)
- Patient load of treating radiotherapy units (based on patient load dring 5 or 10 yrs)
- Tumor structure in imaging (tumor volume, cysts, calcifications)
- Endocrine deficiencies (number of deficient hypothalamic-pituitary axes)
- Growth hormone substitution (patient age at initiation, duration)
- Ophthalmological deficits (visual acuity, perimetric deficits)
- Neuropsychological findings, memory deficits, cognition (HIT-Basisdiagnostikum)

- Eating disorders (IEG)
- Experimental therapeutic approaches for obesity treatment (GLP-1R Agonists, Oxytocin)
- Other experimental therapeutic approaches, e.g. intracavitary therapy (intracystic IFN–α)

4.3. Statistical analysis

The analysis of the data collected in this registry will be mainly descriptive. All inferential analyses will be regarded as exploratory (hypotheses generating) and will be interpreted accordingly. The aim of the analyses is to describe the frequency and modality of treatment approaches and to investigate their influence on survival and QoL. Since the planned study is a purely observational study, no randomized comparisons of treatment strategies are possible. Therefore, in addition to univariable analyses, multivariable analysis strategies are used to take account of different baseline risks due to different demographic or diagnostic characteristics. The model selection in the mutivariable analyses can be done by clinical considerations or by means of automated selection as likelihood-ratio based stepwise selection procedures.

Continuous variables (e.g., BMI SDS, QoL) will be summarised using the following descriptive statistics: n (non-missing sample size), number of missing values, mean, standard deviation, median, Q25%, Q75%, maximum and minimum. Histograms or boxplots will be used for graphical presentation of data. For the comparison of independent groups, statistical tests appropriate to the statistical distribution of the particular endpoint will be used (e.g., Student's t-test, Mann-Whintey U-test). To assess the difference of measurements between two different time points, statistical tests as Student's t-test for paired samples, Wilcoxon signed-rank test, or the sign-test will be applied. For comparison of more than two successive measurements, methods accounting for intra-individual correlation will be used (e.g., Linear Mixed Models), additionally adjusting for potential confounders.

Time-to-event endpoints as OS and PFS will be analysed descriptively using the Kaplan-Meier method. Groups will be compared using the log-rank test. Multivariable analyses will be performed using Cox proportional hazard regression analysis.

For categorical variables, the frequency and percentages (based on the non-missing sample size) of observed levels will be reported. Bar charts will be used for graphical presentation of data. The association of a categorical outcome and categorical independent variables will be analyszed using Fishr's exact test or the χ^2 test.

4.4. Treatment of missing values and outliers

For the primary analyses no imputation of missing values will be applied. Number of patients with missing data and missingness patterns will be presented descriptively. In additional sensitivity analyses multiple imputation approaches or models applicable to longitudinal data with missing values (e.g., linear mixed models) can be used. Results will be compared and discussed. In case of time-to-event enpoints missing data will be treated as right-censored.

4.5. Software

Statistical analyses will be performed using standard statistical software like SAS or SPSS.

5. Documentation

Of particular importance is the grading of preoperative hypothalamic involvement and post-operative assessment of hypothalamic lesions by pre and postoperative imaging (MRI + as needed native CT)!

Documentation is oriented towards standardization of data collection already initiated in KRANIO-PHARYNGEOM 2000 and HIT-ENDO. It consists of:

Registration forms for German Childhood Cancer Registry
These forms are available at the particpating centers. There is one registration form for all malignant diseases as well as for all central nervous system (CNS) tumors (regardless of ranking), which should immediately be sent to the Institute for Medical Biometrics, Epidemiology and Medical Informatics (DKKR), Mainz. DKKR will then send the craniopharyngioma assessment forms to the centers.

Craniopharyngioma assessment forms
Craniopharyngioma assessment forms in KRANIOPHARYNGEOM Registry 2019 should be filled out and then sent to the study's administration. They should include: patient age, preoperative symptom(s), symptom(s) duration, patient's anthropometric data, patient's endocrine condition, primary tumor location and size, surgical strategy (intended complete/incomplete resection), and size of any postoperative residual tumor remnant.

Data assessment forms (see also Appendix section16)
- Data of Diagnosis (CRF 1)
- Neurosurgery Recording Form (CRF 2)
- Radiotherapy Recording Form 1.0 – General Information (CRF 3)
- Radiotherapy Recording Form 1.1 – Treatment Technique (CRF 3)
- Consignment bill sending radiological Images to the Radiological Reference Center Augsburg (CRF 4)
- Follow-up Recording Form (CRF 5)
- Status, Relapse and Death (CRF 6)
- Radiological Reference Evaluation Recording Form (CRF 7)
- Report of serious adverse events Recording Form (CRF 8)

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

Reference histology: Reference-assessed histological findings will be sent to the corresponding pathologist/neuropathologist, the recruiting hospital, and study coordinator.

Reference radiology: Original CT and MRI images of the initial postoperative examination should to be sent via telematik platform (MDPE-Server) to the neuroradiology reference center at University of Augsburg for study evaluation (Dr. B. Bison, Neuroradiology Dept, Universitätsklinikum Augsburg). Imaging for monitoring of suspected progressions should also be sent to the reference center (Augsburg) for co-evaluation.

Reference assessment of imaging will be provided via telematic platform (MDPE).

Archiving study documentation is done by the study coordinator. Data collected in the contex of registration (DKKR) will be archived by the German Pediatric Cancer Registry.

Medical data relevant for the trial KRANIOPHARYNGEOM Registry 2019 will be documented by qualified staff at the participating sites. Data locally assessed will be documented soon after assessment into the eCRF. Entering data may be delegated to qualified members of the team. However, CRFs will be finally signed by an investigator.

The KRANIOPHARYNGEOM Registry 2019 coordinating office at Oldenburg is responsible for the data management of the registry. During data entry at the sites, automated plausibility checks are run. In addition, qualified staff at the KRANIOPHARYNGEOM Registry 2019 trial office will regularly check data

entries for plausibility and completeness. Discrepancies and implausabilities will be solved with the participating sites by queries.

6. Proposed preoperative diagnostics

All suggestions for pre and postoperative diagnostics, treatment and follow-up care are based on the official guidelines (AWMF-No: 025/026) on childhood-onset craniopharyngioma (for detailed information see Appendix section 21)

6.1. Checklist: Preoperative diagnostics

Anthropometric data

- ❍ weight
- ❍ height
- ❍ waist circumference
- ❍ Tanner puberty stage (PH I-IV, B I-IV)

Ophthalmological staus

- ❍ visual acuity
- ❍ optic nerve and optic disc examination
- ❍ visual field

Neuroradiological Imaging

- ❍ MRI before and after contrast agent
- ❍ CT limited scans of the sellar area without contrast agent

Laboratory testing

- ❍ diabetes insipidus diagnostics (fluid intake / urine output, 1st morning urine osmolality
- ❍ serum prolactin
- ❍ α_1-fetoprotein and β-hCG in serum
- ❍ thyroid parameters (fT4, TSH)
- ❍ serum/salivary cortisol profile or free cortisol in 24h urine collection

Documentation forms (see CRFs - Appendix section 16)

Functional capacity

- ❍ Fertigkeitenskala Münster-Heidelberg (FMH)

Neuropsychological assessment if feasible (basisdiagnostikum of HIT trials)

- ❍ 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)
- ❍ specific neuropsychological assessment (s. page 47)

Quality of life (if possible!)

- ❍ PedQol 8 – 18-yr or 4 – 7-yr (patient and parent version)
- ❍ PedsQL (patient and parent version)

Intraoperative asservation of CSF, cyst fluid, tissue for tumor bank

6.2. Highly recommended diagnostics at primary diagnosis

Register procedure	Parameters
clinical neurological findings	
native MRI + gadolinium	tumor dimensions
native CT	calcifications
ophthalmological findings	field of vision, vision acuity, papilledema
anthropometric examination	height, weight, body mass index (BMI), Tanner pubertal stage
laboratory diagnostics	prolactin, α-fetoprotein, β-hCG, fT4, TSH Desmopressin (DDAVP) test for central DI

6.3. Optional diagnostics at primary diagnosis

Optional procedures	Parameters
endocrine testing	preoperative endocrine deficits
neuropsychological diagnostics	preoperative baseline assessment
QoL (PedQol)	preoperative baseline assessment

Objectives of preoperative diagnostics

- Imaging confirmation of suspicious diagnoses as well as differential diagnosis with 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 hormonal substitution treatment (DI, hypocortisolism)
- Ophthalmological assessment of vision acuity, field of vision and existence of papilledema
- Baseline assessment of preoperative conditions (anthropometry, neuropsychology and health-related QoL)

Anamnesis

Preoperative information on patient history as well as parental auxiological case histories should be compiled (see MARWIN forms).

Clinical findings / anthropometric data

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

b. Anthropometric measurements
Height and weight:

- Patient's **height** should be measured in upright standing position using a stadiometer. Baby and infant length measurement (up to 2-yrs of age) is taken while baby/infant is in lying position. Height/length value is averaged based on three consecutive measurements.

- Waist circumference should be measured midway between the lowest rib and the top of the iliac crest at the end of gentle expiration. Circumferences were measured over the naked skin and noted to the nearest 0.1 cm. Infants were measured in the supine position.

6.4. Proposed preoperative neuroradiological imaging

Magnetic resonance imaging (MRI)
Cerebral MRI with and without contrast enhancement is the preferred neuroradiological technology for for primary diagnosis of 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 slices)
- Proton-weighted and T2-weighted axial images of the entire brain

After gadolinium enhancement:
- T1-weighted images, coronary and sagittal, as taken in pre-contrast enhancement images
- T1-weighted axial images as done for T2

Computerized tomography (CT) of the sellar area
CT is specifically used to identify calcifications frequently found in craniopharyngiomas. Because calcifications are **not** detectable in MRI, identifying their existence and location using CT is absolutely key to planning of surgical access and operative approaches. Another essential use of CT is the differential diagnostic assessment of craniopharyngioma vs. astrocytoma by calcification verification. For the reasons just described, preoperative CT verification of calcification localization is a highly proposed diagnostic consideration.
As a rule, postoperative native, non-enhanced CT monitoring should be carried out so that any eventual residual tumor calcifications can be identified. If preoperative CT has definitively ruled out the existence of calcifications, postoperative CT can be waived. Early postoperative MRI (within first 48 to 72 hours) is not required as craniopharyngioma are extraaxial cerebral tumors. First postoperative MRI for assessment of residual tumor and the degree of resection should be performd 2-3 month after initial surgery.

For routine follow-up monitoring, MRI **without** contrast agent (gadolinium) is recommended. When MRI is not available, CT without contrast agent can be used on a very exceptional basis for follow-up course monitoring. However, the cumulative lens dosage in follow-up CT examinations needs to be paid close attention to.

Original images of the following examination series should, along with the local radiologist findings, be sent to the KRANIOPHARYNGEOM Registry 2019 neuroradiology reference center (Department of Neuroradiology, Dr. B. Bison, Universitätsklinikum Augsburg) via telematic platform:

- Preoperative MRI and CT
- Postoperative MRI and CT if used (depending on preoperative calcification verification)

The following neuroradiological reference center-defined assessment parameters will be provided by the neuroradiological reference center:

Grading of preoperative hypothalamic involvement and surgical hypothalamic lesions
The degree of hypothalamic involvement / surgical lesion will be evaluated as published [33, 64]: grade 0 (zero degree), no hypothalamic involvement / surgical lesion; grade 1 (first degree), hypothalamic involvement / surgical lesion of the anterior hypothalamus not involving the mammillary bodies and the hypothalamic area beyond mammillary bodies; and grade 2 (second degree), hypothalamic involvement / surgical lesion of the anterior and posterior hypothalamic area, *i.e.* involving the mammillary bodies and the area beyond mammillary bodies.

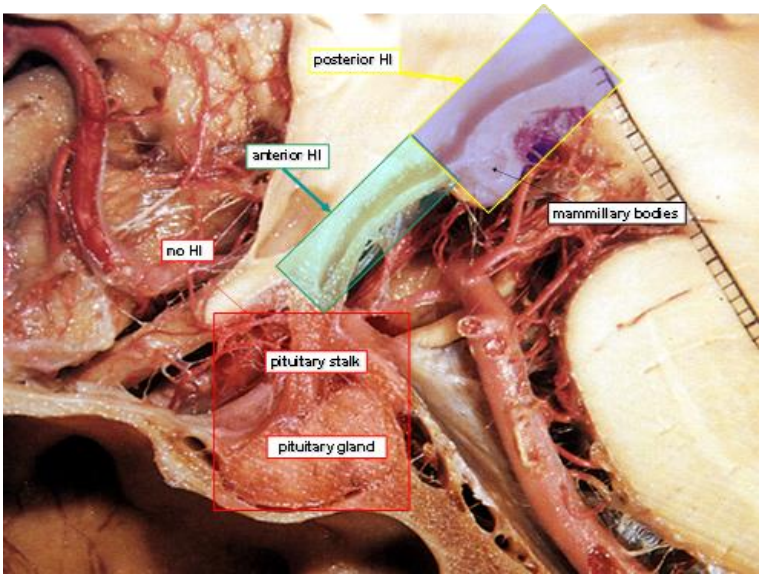

Figure 6: Anatomical situs with depiction of areas relevant for grading of hypothalamic involvement/lesions (courtesy J. Flitsch)

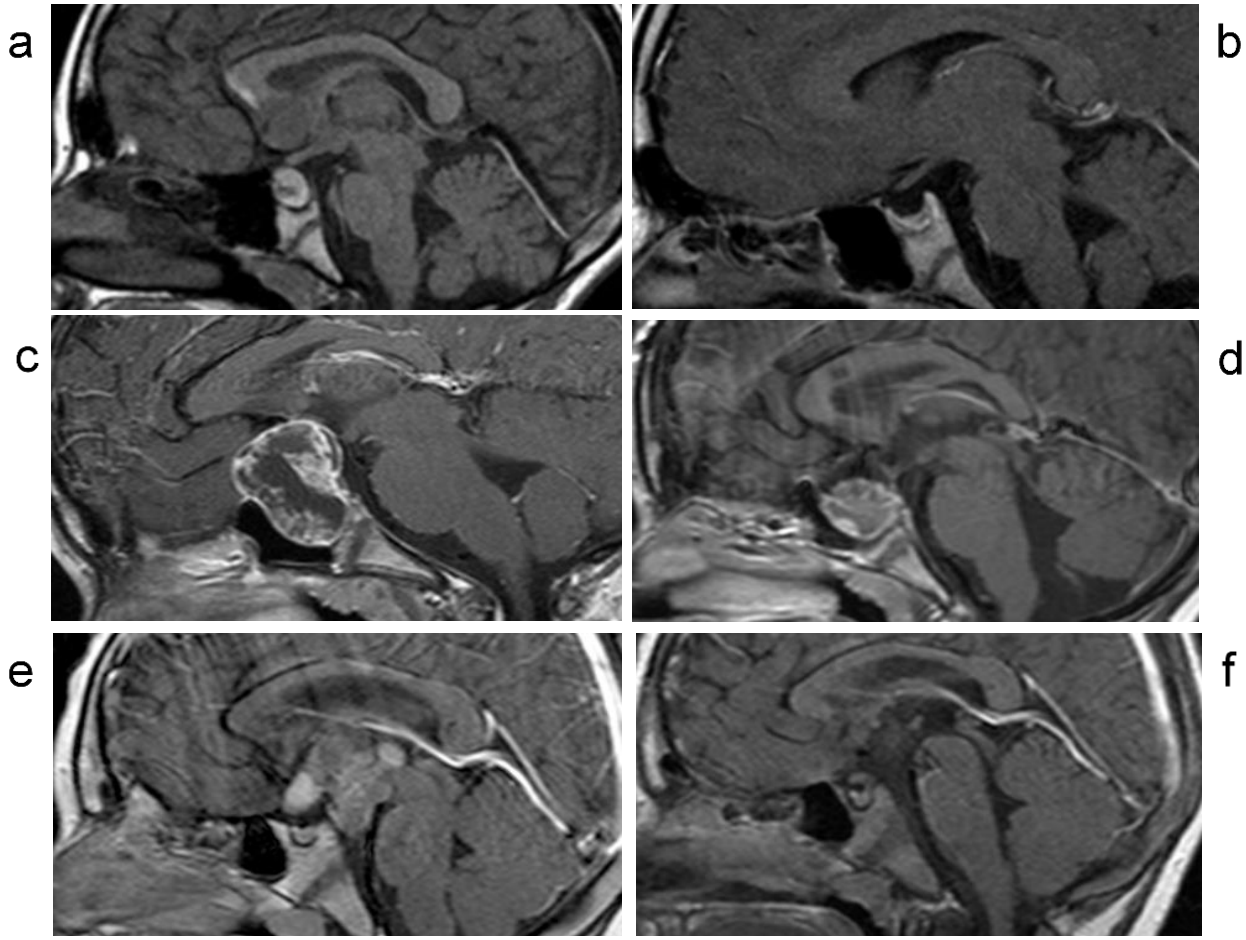

Figure 7: MRI imaging before and after surgery in three cases of childhood craniopharyngiomas (CP) with different grade of hypothalamic involvement/lesion. (a and b) Patient with CP confined to the intrasellar space (grade 0 = no hypothalamic involvement (a)/ no surgical lesion (b)). (c and d) Patient with CP involving the anterior hypothalamus (grade I = hypothalamic involvement (c)/ surgical lesion of the anterior hypothalamic area (d)). (e and f) Patients with CP involving the anterior and

posterior hypothalamus (grade II = hypothalamic involvement (e)/ surgical lesion of the anterior and posterior hypothalamic area (f)). Mammillary bodies are defining the border betreen anterior and posterior involvement/ lesion. (Müller *et al.*, Nat Rev Endocrinol, 2017) [3].

6.5. Proposed preoperative ophthalmologic diagnostics

Visual acuity, retina, and optic disk examination (papilledema evaluation), field of vision assessment (Goldman perimeter or computerized perimetry), ocular motility (cover test), plus optional color vision test (Ishiara or Matsubaro plates) and collimated light-emitting target test are recommended.

6.6. Proposed preoperative neuropsychological examinations

Preoperative neuropsychological diagnostics are recommended only when patient is in good clinical condition (no signs of increased intracranial pressure, headaches, or reduced general condition) and surgery should not be delayed for preoperative neuropsychological examinations. Preoperative diagnostics yield 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.

6.7. Proposed preoperative laboratory diagnostics

- Serum and urine osmolality (1st morning urine)
- Serum electrolytes, creatinine, uric acid, monitoring of fluid intake / urine output
- Plasma coagulation parameters
- Serum concentrations of prolactine, α-fetoproteine, β-hCG
- Thyroid parameters (fT4, TSH)
- Serum or salivary cortisol in daily profile or free cortisol in 24h urine collection
- DDAVP test (only if feasible before surgery)

6.8. Proposed preoperative endocrine diagnostics

Central DI:

Increased serum sodium concentrates along with increased serum osmolality in concert with decreased urine osmolality points to central DI, its presence indicated by failures in normal serum osmolality and the kidney's ability to maintain normal urine concentrations (urine weight >1020 g/l, urine osmolality > 750 mOsm/kg H_2O and/or ratio of urine/serum osmolality >2). The DDAVP test specifies and distinguishes differences between central and renal DI when DI is suspected. However, DDAVP testing is only recommended for patients in clinical stable condition without implicating any delays in surgical treatment. DDAVP substitution (nasal or parenteral administration – see section on pharmaceutical treatments) is recommended after diagnosis of central DI.

Hypocortisolism

Every craniopharyngioma patient is at potential risk of clinical complications due to hypocortisolism preoperatively and at an even higher risk perioperatively. Even if preoperative lab tests have excluded hypocortisolism (normal findings for cortisol in circadian serum/saliva profiles and 24h urine collection cortisol), hydrocortisone substitution in stress dosage should be preoperatively administered (increase normal substitution dose [10–15 mg/m² body surface area (BSA)/d] 3–4 times, i.e. 30–50 mg/m² BSA/d). Hydrocortisone substitution is not necessary when dexamethasone prophylaxis is administered perioperatively. When dexamethasone therapy is administered perioperatively, hydrocortisone substitution should be intiated postoperatively.

Hypercortisolism

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

Hyperprolactinemia

Extremely elevated basal serum prolactin levels (>250 µg/l, >5000 mU/l) indicate a prolactinoma. Slight serum prolactin elevations are consistent with the presence of a craniopharyngioma.

Increased levels of α_1-fetoprotein and β-hCG in serum/CSF

Elevated levels of α-fetoprotein and β-hCG (human chorionic gonotropin) 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 coordinator: Dr. G. Calaminus, University Hospital Bonn). Unambiguously increased tumor markers in the serum and/or CSF spare the patient from invasive diagnostic surgery for histological confirmation.

Hypothyroidism
In secondary hypothyroidism, peripheral thyroid hormones (free T_4, fT4) are lower or in the lower end of the standard range (basal secretion). TRH test: in secondary pituitary hypothyroidism, TSH release response is diminished or even absent following TRH administration; a different reaction pattern is found in tertiary hypothalamic hypothyroidism (see test protocol).

Growth hormone (GH) deficiency
Lowered serum concentrations of IGFBP-3 (insulin-like growth factor-binding protein 3) or IGF-I (insulin-like growth factor 1) substantiate suspicion of growth hormone deficiency. Further diagnostics (GH stimulation tests 6 month after surgery) and substitution therapy are not recommended before surgery and should never delay surgery.

Growth hormone excess
Significantly elevated 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 GH-suppression caused by increased blood sugar.

Hypogonadism
Reduced serum sex steriod concentrations (estrogen, testosterone) and/or basal gonadotropines (LH - luteinizing hormone, FSH - follicle-stimulating hormone) substantiate the suspicion of secondary or tertiary hypogonadism in pubertal and adult patients. Further preoperative diagnostics such as introduction of substitution therapy are not necessary and should never delay surgery. In prepubertal patients, low concentrations of sex steroid and gonadotropine serum concentrations are physiological findings. Craniopharyngioma patients should be spared measuring these parameters until after surgery.

7. Pathology

Due to the difficulties encountered in making an exact brain tumor diagnosis in children, the registry 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) at University of Bonn. All blocks will be returned prompty after processing. The material will be examined using conventional light-microscopic assessment 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 study and sent to both the local pathologist and the study coordinator. 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 (world health organization) tumor classification criteria of the newest version of WHO tumor classification.

Reference pathologist:

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

Biocase dry ice transport boxes available at the pediatric oncological departments 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 tumor tissue specimen for reference DNA analyses.
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 Registry 2019.

8. Proposed postoperative diagnostics

All suggestions for pre and postoperative diagnostics, treatment and follow-up care are based on the official guidelines (AWMF-No: 025/026) on childhood-onset craniopharyngioma (for detailed information see Appendix section 21)

8.1. Checklists: Postoperative diagnostics

	3 mo post OP	4–6 mo post OP	___th yr (annual checkup)
History			
Interim anamnesis	❍	❍	❍
Clinical examination			
Anthropometric measurements	-	❍	❍
Neurological status	❍	-	❍
Ophthalmological status	❍	-	❍
Neuropsychological evaluation			
HIT-Basisdiagnostikum (s. page 45)	❍	-	❍
Specific neuropsychological evaluation (s. page 46)	❍	-	❍
Quality of life (PedQol , PedsQL)	❍	-	❍
Functional capacitiy (FMH)	❍	-	❍
Lab tests			
Baseline endocr. status (fT4, TSH, Cortisol, IGF-I)	-	❍	❍
Stimulation testing (at 6 Mo post OP)	-	❍	❍
Imaging diagnostics			
Cranial MRI	❍	-	❍
Cranial CT (as needed, i.e. calcifications)	❍	-	❍
Documentation			
Status assessment (see CRFs in appendix)	-	-	❍
Course documentation (see CRFs in appendix)	-	-	❍

For performed therapies

❍ Radiation Therapy Technique
❍ Radiological Reference Assessment
❍ Radiological monitoring of residual tumor every 3 mo

8.2. Overview of suggested postoperative diagnostics

	Instrument	Timing	
		post-OP	frequency
QoL (HIT-Leben)	PedQol, PedsQL	3 rd mo	1 × / yr
Clinical neurological findings		3rd mo	1 × / yr
Neuroradiological imaging	MRI + as necessary CT	3rd mo	3-6 mo
Ophthalmological findings	FoV, acuity, papilledema	3rd mo	1 × / yr
Anthropometric examination	height, weigh	3rd mo	1 × / yr
Endocrine deficiencies	endocrinology	6th mo	1 × / yr
Functional capacity	FMH	3rd mo	1 × / yr
Neuropsychological status	see instruments	3rd mo	1 × / yr
Body composition (only for obese patients with BMI>3SD)	(pages 45, 46) DEXA		every 2 yrs

FoV: field of view; DEXA: **D**ual-**E**nergy **X**-ray **A**bsorptiometry; mo: month; yr: year

Laboratory diagnostics

These encompass perioperative, intense monitoring of electrolytes and osmolality in order to diagnose acute osmolality pathologies (central DI and syndrome of inadequate ADH (antidiuretic hormone) secretion). Early detection of polyuria/polydypsia DI phases, fluid regulation titration using i.v. infusion, NaCl substitution, and DDAVP venous infusion (see section on postoperative pharmaceutical treatments).

8.3. Suggested neuroradiological postoperative follow-up monitoring

Immediate postoperative course

- **MRI** before and after gadolinium enhancement. Early postoperative MRT examinations (within the first postoperative 48–72h) are not required.
- **Imaging data are to be sent via telematik platform for neuroradiological reference assessment to** Dr. Bison, Augsburg, Germany.

Long-term postoperative course

- **No residual tumor after resection**: MRI monitoring without gadolinium enhancement every 3–**6 month during 1st yr** and every 6–**12 month afterwards** up until 5 yrs following surgery.

- **Residual tumor/calcifications after resection**: MRI with contrast enhancement every **3 month during 1st yr** and annually for the first 5–8 yrs following surgery.

- **Based on clinical status** the indication for short-term, imaging course monitoring **always** arises

Radiological reference assessment suggests the following imaging:

- pre and postoperative MRI for all patients
- preoperative CT without contrast enhancement for all patients

8.4. Ophthalmological course monitoring

Every 3–6 month ophthalmological examinations of retina, acuity and visual field are necessary during the first and second yr after surgery and annually afterwards.

8.5. Anthropometric course monitoring

Body height/length, weight, Tanner puberty stage, and testicle volume using Prader's orchiometer should be measured annually during follow-up. Left hand carpogram x-ray examinations using the Greulich and Pyle method for estimation of bone age should be performed annually.

8.6. Functional capacity evaluation instruments

Functional abilities assessment questionnaire (FMH)

Wolff *at al.* developed and published a German questionnaire (FMH) in 1978 [303] to measure QoL and functional capacity of patients with brain tumors. The FMH scale includes 57 questions expressing the quality and independence level of daily life. The average time to answer the questionnaire is 4.5 minutes (min) [303]. The FMH scale was normalized using 971 test subjects (45% 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 IQ exists, 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. The FMH scale is a diagnostic component of the GPOH trials SIOP LGG (low-grade glioma) and SIOP HGG (hypothalamic-chiasmatic glioma). Prospective, multicenter evaluations using the FMH scale make comparisons possible between craniopharyngioma patients and patients with LGG of comparable anatomical localization.

8.7. Neuropsychological evaluation instruments – course monitoring by ND-POH

COGNITIVE DOMAINS	
Intelligence (fluid)	• CPM (3; 9 bis 10; 11 Jahre) • SPM (11; 0 bis 20; 11 Jahre) • APM (ab 21 Jahre) oder • Raven's 2 (4; 0 bis 69; 11 Jahre)
Intelligence (crystaline)	• • WISC-IV – Untertest *Passiver Wortschatz* (3; 0 bis 5; 11 jahre) • WISC-V – Untertest *Wortschatztest* (6; 0 bis 16; 11 Jahre) • WAIS-IV – Untertest *Wortschatztest* (ab 17; 0 Jahre)
Visuomotor	• Beery VMI (ab 2; 0 Jahren)
Short-term memory-/Arbeitsgedächtnis	• K-ABC-II – Untertest – *Zahlen nachsprechen* (3; 0 bis 5; 11 Jahre) Jahre) • WISC-IV – Untertests *Zahlen nachsprechen vorwärts*, *Zahlen nachsprechen rückwärts*(6; 0 bis 16; 11 Jahre) • WAIS-IV – *Zahlen nachsprechen vorwärts*, *Zahlen nachsprechen rückwärts* (ab 17;0 Jahre)
Feinmotorik	• Purdue Pegboard (ab 5;0 Jahren)
Verarbeitungs-geschwindigkeit	• WPPSI-IV – Untertests *Symbole kodieren, Symbolsuche* (4;0 bis 5; 11 Jahre) • WISC-V – Untertests *Zahlen-Symbol-Test*, *Symbolsuche* (6; 0 bis 16; 11 Jahre) • WAIS-IV – Untertests *Zahlen-Symbol-Test*, *Symbolsuche* (ab 17;0 Jahren)
Lern- und Merkfähigkeit	• Verbaler Lern- und Merkfähigkeitstest (ab 6 Jahren)
Aufmerksamt	• TAP (ab 6 Jahren) – Untertests *Alertness*, *Geteilte Aufmerksamkeit, Go/NoGo*
QUESTIONNAIRES	
Executive Function	• Behaviour Rating Inventory of Executive Functioning – Preschool Version / Verhaltensinventar zur Beurteilung exekutiver Funktionen für das Kindergartenalter (BRIEF-P; 2 - 6 Jahre) • Behaviour Rating Inventory of Executive Functioning / Verhaltensinventar zur Beurteilung exekutiver Funktionen (BRIEF; 6 - 16 Jahre;)
Fremdbeurteilung	• Fragebogen zur Erfassung kognitiver Prozesse bei 4-6-jährigen Kindern (KOPKI 4-6;4 bis 6

kognitiver Probleme	Jahre) • Kognitive Probleme bei Kindern und Jugendlichen (KOPKIJ) (6 - 16 Jahre)

ND-POH

Anmerkungen. CPM: Raven's Coloured Progressive Matrices; SPM: Raven's Standard Progressive Matrices; APM: Raven's Advanced Progressive Matrices; WPPSI-IV: Wechsler Preschool Primary Scale of Intelligence 4th Edition; WISC-V: Wechsler Intelligence Scale for Children 5th Edition; WAIS-IV: Wechsler Adult Intelligence Scale 4th Edition; K-ABC-II: Kaufman Assessment Battery for Children 2nd Edition; Beery VMI: Beery-Buktenica Developmental Test of Visual-Motor Integration 6th Edition; VLMT: Verbaler Lern- und Merkfähigkeitstest; TAP: Testbatterie zur Aufmerksamkeitsprüfung.

The tests recommended are identical for all patients with pediatric brain tumors and published as the ND-POH used in trials of the HIT network. The tests are recommended for estimating mental, sensory-motor, and fine motor functions three month following surgery and during annual postoperative examinations. Selection of meaurements takes into consideration important key factors of stratums 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.
Neuropsychological testing should only be carried out at 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 GBA resolution and test result data are to be made available to study coordinator.

Recommended additional questionnaires for assessment of specific domains frequently affected in craniopharyngioma patients:

Domain	Questionnaires: Original (If applicable) and German Version	Age range (yrs)	Self or external rating
Depression	**Children's Depression Inventory** (**CDI;** Kovacs, 2003 [304]). German version: Depressionsinventar für Kinder und Jugendliche (DIKJ) by Stiensmeier-Pelster *et al.* [305].	8-16	self
Anxiety	**Kinder-Angst-Test (KAT-III)** by Tewes & Neumann [306]	6-18	self
Quality of Life	**Pediatric Quality of Life Inventory** (**PedsQL)** by Varni *et al.* [307]	2-18	self* external
Daytime Sleepiness	**The Epworth Sleepiness Scale for Children (ESS-C)** [33] German version of the ESS-C by Handwerker *et al.* [308].	6-18	self*
Narcolepsy	**The Ullanlinna Narcolepsy Scale (UNS)** by Hublin *et al.*, [309] A German version, adapted for children and adolescents is available in Handwerker *et al.* [308].	6-18	self*
Fatigue	**The PedsQL™ Multidimensional Fatigue Scale (PedsQL–MFS)** by Varni *et al.*, [307], German version by Jung *et al.* [310]	5-18	self & external
Apathy	**Apathy Evaluation Scale (AES)** by Marin *et al.*, 1991 [311], German version by Lueken *et al.* [312]. Self-rating (AES-S) and informant ratings (AES-I)	6-18	self & external
Eating behavior	**Inventar zu Essverhalten und Gewichtsproblemen** by Diehl *et al.* **(IEG-Kind)** [313]	6-18	self
Physical Activity	**MoMo-AFB** by Bös *et al.* 2009 [314]**.**	6-18	self
Behavior	**Child Behavior Checklist (CBCL) and the Youth Self Report (CBCL, YSR)** by Achenbach *et al.*, 1991 [291]. German version by Döpfner *et al.* 2014	11-18 6-18	self external

Social Responsiveness	**Social Responsiveness Scale (SRS)** by Constantino *et al.*, 2007 [315]. German version: Skala zur Erfassung sozialer Reaktivität (SRS) by Bölte *et al.* [316]	4-18	external
Emotion Regulation	**Fragebogen zur Erhebung der Emotionsregulation bei Kindern und Jugendlichen (FEEL-KJ).** German version by Grob & Smolenski, 2005	10-20	self

***** It is recommended to additionally involve caregivers in the completion of the questionnaire

Description of recommended questionnaires:

Depressionsinventar für Kinder und Jugendliche (DIKJ), by Stiensmeier-Pelster *et al.*, 2014 [305]. German version of the Children's Depression Inventory (CDI; Kovacs, 2003 [304]), used to measure the intensity of self-rated depressive symptoms in children and adolescents (8-16 yrs). The recent third edition contains 29 items, each of which requires to choose between three alternatives (from 0 to 2) to indicate the participant's thoughts and feeling in the last time, covering all relevant symptoms of depression (Major Depression according to DSM IV (diagnostic and statistical manual of mental disorders)). All scores are summed up. Completion time: 10-20 min.

Kinder-Angst-Test (KAT-III), Tewes, A. & Neumann, A. (2000) is a German scale to measure anxiety in children and adolescents aged 6-18 yrs. The inventory consists of three forms for self-rating, covering two different aspects of anxiety: trait and state anxiety. Form A is used to assess trait anxiety and requires participants to affirm or negate 20 statements addressing how they generally feel (e.g., *I often feel anxious.*). The remaining forms are used to assess state anxiety prospectively, i.e., related to a forthcoming stressful event (Form P, e.g., *I am worried about what will happen now*) and retrospectively (Form R, e.g.). The latter forms consist of a 10-item state scale, requiring yes/no ratings. An additional form allows for an exploration of parents' perception of their children's anxiety symptoms. We will use Form A and P, which requires a completion time of 5-10 min.

The Epworth Sleepiness Scale for Children (ESS-C) by M.C. Melendres *et al.* 2004 [317] is the child version of the 8 item original version for adults (ESS) and measures self-perceived daytime sleepiness by using statements related to falling asleep in daytime situations. A German version of the ESS-C is provided by Handwerker *et al.*, 2007 [308]. The child version has seven of the original items plus a replacement item. Items are adapted to children aged 6-18 yrs. (e.g. how likely are you to falling asleep whild doing homework or taking a test instead of falling asleep in a car, while stopped for a few min in the traffic. A sum score of >8 in children and a score of >13 in adolescents is considered abnormal. Completion time: < 5 min.

The Ullanlinna Narcolepsy Scale (UNS) by Hublin *et al.*, 1994 [309] is used to measure symptoms related to narcolepsy, including frequency of daytime narcoleptic episodes, muscle weakness associated with powerful emotions, and time to fall asleep in the evening. Participants (6–18 yrs) score every item from 0 (never) to 4 (frequently), resulting in a score between 0 and 44 points. Subscores of the 11 items scale can also be obtained for the two main features of the narcoleptic syndrome: the abnormal sleeping tendency and cataplexy. A German version, adapted for children and adolescents is available in Handwerker *et al.*, 2007 [308]. A narcolepsy score of >14 in adults and adolescents is considered abnormal. For children, it is recommended to additionally involve their caregivers in the completion of the questionnaire. As the diagnosis of cataplexy is in particular difficult in younger age, the cut-off score is not generally recommended for children. Completion time: < 5 min.

The PedsQL™ Multidimensional Fatigue Scale (PedsQL–MFS), German version by Jung *et al.*, 2009) [310] is an instrument to measure fatigue in pediatric populations. It is a supplementary module to the PedsQL™ 4.0 Generic Core Scales [318], but can be used independently. The 18-item scale was first developed by Varni *et al.*, 2002 [307] and consists of three subscales: (1) General Fatigue (6 items, e.g., "I feel too tired to do things that I like to do."), (2) Sleep/Rest related Fatigue (6 items, e.g., "I rest a lot."), and (3) Cognitive Fatigue (6 items, e.g., "It is hard for me to keep my attention on things."). Participants are instructed to indicate how much of a problem each item has been during the past one month. The instrument uses a five-point Likert scale, which is transformed into a scale from zero to 100 (1=100, 2=75, 3=50, 4=25, 5=0). Higher scores indicate lower fatigue symptoms. The PedsQL-MFS has versions for self-reports from children and adolescents (5-7 yrs; 8-12 yrs; 13 to 18 yrs) and a version for reports from parents (2-18 yrs). Completion time: 5 min.

Apathy Evaluation Scale (AES) by Marin *et al.*, 1991 [311], German version by Lueken *et al.*, 2000 [312]. The AES is an 18-item scale that assesses behavioral, emotional, and cognitive aspects of

apathy. Each item (e.g., she gets things done during the day) is rated on a 4-point Likert scale (not at all, slightly true, somewhat true and very true). The total score ranges from 18 to 72 points and higher scores indicate more severe apathy. In the original version, a total score > 37 indicated clinical presence of apathy. The AES has a self-report version (AES-S), an informant version (AES-I) and a clinician version (AES-C). Self-ratings can be obtained from children >12 yrs of age. Informant ratings for 6-18 yrs. Completion time: 5 min.

Inventar zu Essverhalten und Gewichtsproblemen (IEG-Kind)", by Diehl *et al.*, 1999. A German questionnaire, with well-established psychometric properties, used to assess eating attitudes, eating behavior and/or putative problems with body weight, especially in obese patients (6–18 yrs). The inventory is structured into 14 behavioral dimensions, which represent an in-depth view of the person's or group's psychological outlook towards food (questions are answered by a personal interpretation of the question). The IEG contains additional scales assessing eating disorders. These scales are used to analyze symptoms associated with eating disorders. The Inventory for Eating Disorders (ESI) is structured into nine behavioral dimensions, these behavior dimensions representing an in-depth view of the person's or group's symptoms, such as binge eating, nausea, vomiting, associated with eating disorders. Completion time: appr. 30 min.

MoMo-AFB by Bös *et al.* [314]. A German questionnaire, which is an alternative for the well-validated **International Physical Activity Questionnaire (IPAQ)**, when working with children and adolescents (6–18 yrs). The Momo-AFB consists of 28 items asking for everyday physical activity, sports within and outside of organised clubs, physical education as well as compliance with physical activity guidelines. Completion time: 10 min.

Verhaltensinventar zur Beurteilung exekutiver Funktionen (German version of the Behavior Rating Inventory of Executive Dysfunctins) by Drechsler & Steinhausen, 2013. The questionnaire aims to assess executive dysfunctions in children aged 6 to 16 yrs. Three forms are available. One for self-rating for children aged 11 to 16 yrs. and two additional, each one for parents and teachers to rate children and adolescents aged 6-16 yrs. The external assessment contains 86 questions. There are two main scales: behavioral regulation (including the scales behavioral inhibition, flexibility and emotional control) and a kognitive regulation scale (including initiative, working memory, planning, organizing, monitoring). Both scales are summed up for an executive functioning score. Self-assessment has a similar form. 10-15 min.

Child Behavior Checklist (CBCL/6–18). Parent questionnaire regarding child's/adolescent's behavior by Achenbach *et al.* [291]. German version by Döpfner *et al.*, 2017. The questionnaire is used to rate 6–18 yrs old childrens' competences, observable behavioural features, and observable emotional features. The child's/adolescent's competences are surveyed in the first part of the questionnaire. The second part of the questionnaire contains 120 Items describing the child's/adolescent's observable behaviour and emotional traits plus any physical difficulties. Completion time: 20–30 min.

Social Responsiveness Scale (SRS) by Constantino *et al.*, 2007 [315]. German version: Skala zur Erfassung sozialer Reaktivität (SRS) by Bölte *et al.* [316]. The SRS provides a continuous measure of social abilities, to identify children and adolescents (4-18 yrs) with milder autistic impairments or individuals, which are not autistic but suffer from social impairments. The German version consists of a parent questionnaire with 65 items on a 4-point Likert scale. Completion time: 10 min.

Fragebogen zur Erhebung der Emotionsregulation bei Kindern und Jugendlichen (FEEL-KJ). A German questionnaire by Grob & Smolenski [319], used for self-assessment of 15 different emotion regulation strategies in response to anxiety, sadness, and anger. It was designed for 10-20 yrs old children and adolescents and contains 90 items, which have to be rated on a 5-point Liekert scale. Completion time depends on the participants' age and varies from 10-30 min.

8.8. Health-related QoL test instruments

Evaluation form for surveying craniopharyngioma patient life situation

The 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 parental assessment and requires 10 min to complete.

For assessment of quality of life/survival two instruments are used (**PedQol** - Pediatric QoL Questionnaire; German version by G. Calaminus, 2000, and **PedsQL**®) will be used. **PedQol** was used for assessment of QoL in KRANIOPHARYNGEOM 2000/2007 and therefore provides the opportunity of comparison with historical cohorts. **PedsQL**® is used for QoL assessment in the current SIOP brain tumor studies and therefore provides the opportunity of QoL comparison between craniopharyngioma and other pediatric brain tumors.

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. These theoretically-based domains are supplemented by the relevant empirically-based "autonomy" and "physical function" domains. PedQol surveys patient-perceived QoL, providing a patient-reporting instrument for children and adolescents from 8 to 18 yrs 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 yrs 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 closely with the PedQol 8-18 yrs 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 in both healthy and cancerous children. PedQol was used for assessment of QoL in KRANIOPHARYNGEOM 2000/2007 and therefore provides the opportunity of comparison with historical cohorts.

The PedsQL® Measurement Model is a modular approach to measuring health-related quality of life (HRQOL) in healthy children and adolescents and those with acute and chronic health conditions. The PedsQL® Measurement Model integrates seamlessly both generic core scales and disease-specific modules into one measurement system. The 23-item PedsQL® Generic Core Scales were designed to measure the core dimensions of health as delineated by the World Health Organization, as well as role (school) functioning. The PedsQL® instrument is practical and flexible (designed for use with community, school, and clinical pediatric populations). PedsQL® distinguishes between healthy children and children with acute and chronic health conditions (Ages 2-18; Child Self-Report Ages 5-7, 8-12, 13-18; Parent Proxy-Report Ages 2-4, 5-7, 8-12, 13-18). Scales: Physical Functioning (8 items), Emotional Functioning (5 items), Social Functioning (5 items), School Functioning (5 items). Summary Scores: Total Scale Score (23 items), Physical Health Summary Score (8 items), Psychosocial Health Summary Score (15 items). PedsQL is used for QoL assessment in the current SIOP brain tumor studies and therefore provides the opportunity of QoL comparison between craniopharyngioma and other pediatric brain tumors. Completion time < 4min.

8.9. Recommended measuring of body composition (DEXA)

Body scans using the **D**ual-**E**nergy **X**-ray **A**bsorptiometry (DEXA) objectively measure the body's adipose tissue and render a valid obesity grading. DEXA data are an elementary component of investigating incidences of obesity, risk factors and therapy. Regular body composition investigations using DEXA are recommended **every 2 yrs** to monitor development of obesity in patients at risk (BMI>3SD). The total radiation load amounts to ca. 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.

8.10. Proposed endocrine follow-up diagnostics

Schedule of endocrine follow-up diagnostics

	6 mo post OP	1x / yr	every 2 yrs	Comments
Anthropometric	❍	❍	-	height, weight, pubertal stage
carpogram		❍	-	bone age (Greulich & Pyle)
fT4, TSH	❍	❍	-	
IGFBP-3 or IGF-I	❍	❍	-	
cortisol profile of saliva or serum	❍	❍	-	Frequency of endocrine diagnostics during 1st yr post OP should increase as incidental weight increase requires.
or: free cortisol in 24h urine collection	❍	❍	-	
DHEAS	❍	❍	-	
LH/FSH (only pubertal patients)	❍	❍	-	
prolactin	❍	❍	-	
For obese patients				Examinations only for obese (BMI >+3 SD) patients
oGTT	❍	❍	-	
HbA_1c	❍	❍	-	
body composition (DEXA)	❍	-	❍	
Endocrine testing				
CRH / GHRH test	❍	-	-	Endocrine testing performed appr. 6th mo post-OP according to test protocols.
GnRH test (patients >14 y)	❍	-	-	GnRH test for patients >14 yrs of age
GH stimulation test	❍	-	-	

Appr. 6 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 deficiencies. Growth hormone stimulation tests, releasing hormone tests (CRH, GHRH tests and GnRH tests for patients >14 yrs) 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 month postoperatively, tapering off or discontining medication should be rescheduled for sometime later.

Tapering off/discontinuing medication before endocrine diagnostics (6 month post OP)

Hydrocortisone: An abrupt interruption of hydrocortisone medication following a 4-6 month substitution to compensate for suppressed adrenocortical function, even if in recovery, would lead to potential primary hypocortisolism, posing a threat to the patient and therefore inadvisable. Accordingly, dosage should be tapered off starting the 4th postoperative month for non-irradiated patients and under regular, weekly clinical monitoring. Patients whose pituitary had to be resected during surgery are to be spared for these tapering-off attempts and testing diagnostics. 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 conservation and/or preservation, it is recommended to discontinue L-thyroxine medication four weeks before hospital endocrinological diagnostics (basal thyroid gland parameters) in the 6th month following surgery.

In the 1st postoperative year

- anthropometric data (every 6 month)
- bone age according to Greulich & Pyle / carpogram (annually)
- Considering that **weight gain occurs early in 1st postoperative yr in 50% of cases** and develops into severe obesity, monitoring the following parameters during the first 6 month following surgery is recommended:
  - IGFBP-3 or IGF-I
  - Thyroid parameters (fT4, TSH)
  - Cortisol profile in serum or saliva, or free cortisol in 24h urine collection

Starting 2nd postoperative year: annual monitoring

- anthropometric data
- IGFBP-3 or IGF-I, thyroid parameters (fT4, TSH)
- Cortisol profile in serum or saliva, or free cortisol in 24h urine collection
  Interruption of hormone substitution (L-thyroxine, hydrocortison) 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 [320].
- prolactin in serum
- dehydroepiandrosterone-sulfate (DHEAS) in serum
- for obese (BMI>3SD) patients only: HbA_1c, (1x per yr)
  body composition exam. (DEXA every 2 yrs)
- clinical symptoms 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: fluid input/output capacities, especially osmolality in morning urine, serum electrolytes and serum osmolality, DDAVP-test,
- late pubertal development (Tanner PHI, BI, GI in girls ≥ 13-yrs; boys ≥ 14-yrs; premature pubertal development (pubarche: girls < 8-yrs; boys: < 9-yrs) or hypogonadism: sex-respective GnRH tests for estrogen or testosterone in serum
- pathological serum concentrations of IGFBP-3 and/or IGF-I, pathological growth rate or distinct weight increase: growth hormone stimulation testing
- pathological low thyroid parameters (fT4, TSH): L-thyroxine substitution

8.11. Long-term monitoring, suggested diagnostics and documentation of KRANIOPHARYNGEOM Registry 2019 follow-up care (> 1 yr postoperative)

Examination	Program	Timing	CRF / forms
Anthropometric	height, weight, waist circumference	annually	CRF 1
History	see assessment forms	annually	CRF 1
Bone age	X-ray left hand	annually	
Body composition	DEXA (only for obese patients, BMI > 3SD)	every 2 yrs	
Endocrine	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>3SD)	annually	CRF 1
Endocrine (testing)	GH stimulation testing GHRH test, GnRH test, CRH test oGTT (for obese patients BMI>3SD)	only as required	CRF 5
Hormonal therapy (documentation)	substitution based on: growth hormone, L-thyroxine, hydrocortisone, sex steroides, DDAVP	annually	CRF 5
Quality of Life	PedsQL / PedQol instrument	annually	questionnaires sent to patients/clinics
Neuropsychological diagnostics	HIT-Basisdiagnostikum spec. neuropsych. evalution (s. page 46)	preoperative, 3 mo post OP and annually	analyses carried out at centers
Neuroradiology	MRI (routine monitoring w/o gadolinium enhancement)	Every 6–12 mo 5 – 8-yr post OP,	CRF 3
Ophthalmology	acuity, fundus, visual field, when appr: color vision, oculomotor function	min. 1x / yr	CRF 5
Radiooncological follow-up care	Follow-up care after radiation therapy – morbidities	1 x / yr	CRF 6
Rehabilitation	Hospital-provided rehabilitation	as needed: every 1–2 yrs	

9. Proposed long-term evaluation

Every participating clinic, 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. Evaluating long-term consequences of treatment and disease is also an important goal of KRANIOPHARYNGEOM Registry 2019. 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 section: Preoperative diagnostics).

Long-term diagnostic and therapy standardization, evaluation and quality control were chief aims of HIT-ENDO and KRANIOPHARYNGEOM 2000/2007 and are also goals of KRANIOPHARYNGEOM Registry 2019. The following goals have been set in order to develop a long-term care program in accordance with recently published guidelines for follow-up care in patients with pediatric oncological diseases (AWMF guideline):

- standardization of endocrine diagnostics and substitution therapy
- quality control of endocrine, imaging, ophthalmological and neuropsychological follow-up diagnostics
- quality control of hormonal substitution therapy

Data acquisition regarding postoperative endocrine substitution therapy is limited. Hormone substitution dosage data is not included in the scope of KRANIOPHARYNGEOM Registry 2019. Data acquisition is restricted to which hormone axis requires substitution.

Radiooncological follow-up (as required by radiation protection legislation)
All patient examinations must be systematically monitored once a yr by a radiooncologist. The corresponding documentation forms should be filled out and sent to the radiation reference center.

Treatment-associated long-term consequences of radiation therapy for malignant diseases in children and adolescents
Coordinator:Prof. Dr. med. Dr. Diana Steinmann, Medizinische Hochschule Hannover,
Strahlentherapie und spezielle Onkologie, Carl-Neuberg-Str. 1, 30625 Hannover,
Tel.: +49 (0)511 5322574, Fax: +49 (0)511 5322575, E-mail: steinmann.diana@mh-hannover.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) 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 irradiation in childhood and adolescence". See English version website for details: http://www.ro-journal.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 registry. Two months after therapy has ended, radiation therapy and its consequences are examined annually to detect side effects and classified using the RTOG (Radiation Therapy Oncology Group)/EORTC (European Organisation for Research and Treatment of Cancer) score. Tumor-related follow-up care remains the exclusive domain of the responsible pediatrician.

Study-related masurements include the above-mentioned questionnaires and the reporting to KRANIOPHARYNGEOM Registry 2019, therefore the collection and stroing of data and biomaterial. Routine measurements include the tissue sampling, clinical consulation with treating physicians and the reporting to the German Childhood Cancer Registry.

10. Rehabilitation

Treatment and rehabilitation of a craniopharyngioma patient require a multidisciplinary team of pediatric experts in the areas of endocrinology, neuropediatrics, psychology, psychotherapy and physical therapy to assess possible endocrine, neuropsychologic 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:

	Timing	Important considerations
❍ **Emergency medical card**	When patient is discharged from hospital	Provided by support groups
❍ **Information and training of teachers and caregivers**	Before patient is discharged from hospital	DDAVP nasal administration in case of polyuria, oral glucose for hypoglycemia, flexible stress adaptation of hydrocortisone medication (triple dose!)
❍ **Academic psychological diagnostics**	as needed	For choosing appropriate school type
❍ **Home schooling**	as needed	For applying to responsible educational authority for home schooling
❍ **Medical certificate excusing child from certain types of school sports**	When patient is discharged from hospital	As appropriate: excuse from endurance sports, competitive sports, sport instruction without grades. General excuse from school sports is not recommended.
❍ **Support groups**	as needed	Annual family meeting of craniopharyngioma self-help group. For info. and registration: www.kinderkrebsstiftung.de
❍ **Youth seminars**	as needed	Organization for patients > 16 yrs for supporting transition experiences. For info. and registration: www.kinderkrebsstiftung.de
❍ **Internet homepages**	Info & support contacts	www.kraniopharyngeom.de www.kinderkrebsstiftung.de
❍ **Acquiring nursing care insurance**	as needed	Financial aid for the family and/or out-patient care provisions
❍ **Application for severely disabled person pass**	as needed	For income tax exemptions, unemployment support, misc. priviledges
❍ **Nutrition counseling**	as needed	Low fat, fiber-rich food sources
❍ **Advanced nutrition psychological diagnostics**	as needed	Consultation with registry admin. (E-mail: kikra.doku@klinikum-oldenburg.de)
❍ **Psychotherapy for eating disorders**	as needed	Consultation with registry admin. (E-mail: kikra.doku@klinikum-oldenburg.de)
❍ **Physical therapy**	as needed	
❍ **Rehabilitation treatment**	in 1–2 yr intervals	Rehabilitation treatment reviewed as appropriate after diagnosis consideration

11. Support Organization Addresses

Germany:

German support group for craniopharyngioma patients
Internet: http://www.kraniopharyngeom.de

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

Junge-Leute-Seminare
Contact: Frau Kortum, Deutsche Kinderkrebsstiftung
Adenauer-Allee 134, 53113 Bonn, Germany
Tel.: +49 (0)228 6884621, Fax: +49 (0)228 6884644
E-mail: r.kortum@kinderkrebsstiftung.de
Internet: www.kinderkrebsstiftung.de

Stiftung Deutsche Krebshilfe
Buschstr. 32, 53113 Bonn, Germany
Tel.: +49 (0)228 729900, Fax: +49 (0)228 7299011
E-mail: deutsche@krebshilfe.de
Internet: www.krebshilfe.de

knw Kindernetzwerk e.V.
Schiffbauerdamm 19, 10117 Berlin
Tel.: +49 (0)30 25765960, Fax: +49 (0)6021 12446
E-mail: info@kindernetzwerk.de
Internet: http://www.kindernetzwerk.de

BKMF Bundesverband Kleinwüchsiger Menschen und ihre Familien e.V.
Leinestraße 2, 28199 Bremen, Germany
Tel.: +49 (0)421 3361690, Fax: +49 (0)421 33616918
E-mail: info@bkmf.de
Internet: http://www.bkmf.de (website in English as well)

Bundesarbeitsgemeinschaft Selbsthilfe von Menschen mit Behinderung, chronischer Erkrankung und ihren Angehörigen e.V.
Kirchfeldstraße 149, 40215 Düsseldorf, Germany
Tel.: +49 (0)211 310060, Fax: +49 (0)211 3100648
E-mail: info@bag-selbsthilfe.de
Internet: http://www.bag-selbsthilfe.de

Herzenswünsche e.V.
(Verein für schwer erkrankte Kinder und Jugendliche)
Nienkamp 75, 48147 Münster, Germany
Tel.: +49 (0)251 20202224, Fax: +49 (0)251 9878688
E-mail: info@herzenswuensche.de
Internet: www.herzenswuensche.de

Netzwerk Hypophysen- und Nebennierenerkrankungen e.V.
Waldstraße 53, 90763 Fürth, Germany
Tel.: +49 (0)911 97920090, Fax: +49 (0)911 979200979
E-mail: netzwerk@glandula-online.de

Internet: https://www.glandula-online.de

Austria:

St. Anna Kinderkrebsforschung – Children's Cancer Research Institute
Zimmermannplatz 10, 1090 Wien, Austria
Tel.: +43 (0)1 40470 0, Fax: +43 (0)1 404707150
E-mail: spende@kinderkrebsforschung.at
Internet: https://test.treat.agency/ccri/

Verband der Österreichischen Kinder-Krebs-Hilfe Organisationen
Borschkegasse 1/7, 1090 Wien, Austria
Tel.: +43 (0)1 4028899, Fax.: +43 (0)1 402889910
E-mail: oesterreichische@kinderkrebshilfe.at
Internet: https://www.kinderkrebshilfe.at

BKMF Bundesverband Kleinwüchsiger Menschen und ihre Familien e.V.
Griesstraße 2, 4502 St. Marien, Austria
Tel +43(0)7227 20600
E-mail: office@bkmf.at
Internet: https://www.bkmf.at

Netzwerk Hypophysen- und Nebennierenerkrankungen e.V.
Regionalgruppen in Österreich:
Linz
Andrea Schrattenecker
Tel.: +43 (0)676 4328030
E-Mail: linz@hypophyse-nebennieren.at
Internet: https://www.hypophyse-nebennieren.at

Wien
Andrea Schrattenecker
Tel.: +43 (0)676 7082002
E-Mail: wien@hypophyse-nebennieren.at
Internet: https://www.hypophyse-nebennieren.at

12. Ethical and legal considerations

Approval from the appropriate institutional ethical committees must be sought. Approval for the entire study was obtained from the ethical committee of the Medical Faculty at Carl von Ossietzky University of Oldenburg by the study administration. The protocol (Version 3.0) was approved primarily by the ethical committee Carl von Ossietzky University of Oldenburg, Germany. The register coordinator is required to inform the ethical committee of any issues and/or protocol changes that arise, in accordance with local requirements. Future questions and studies based on the samples and data used in this study will be submitted as new applications to the ethics committee.KRANIOPHARYNGEOM Registry 2019 is conducted in accordance with the revised Declaration of Helsinki – 64th General Assembly, Fortaleza, Brazil, October 2013..

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 fulfill 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:

- Participation in the registry is voluntary at any time
- The consent of the patient or legal guardian can be withdrawn at any time without giving reasons and without resulting disadvantages for further medical care
- 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 patient and legal guardian will be informed in writing and verbally before the start of their registry participation about the scope of the planned scientific investigation and in particular about the possible benefits of the registry and any risks. Their consent will be documented by signing the respective consent form. In case of withdrawal from the registry, data and biomaterial already obtained will be destroyed or the patient / legal guardian will be asked whether he/she agrees to the evaluation of the material.

In this registry, all data are treated confidentially.
In the context of diagnosis, central clinical data of patients will be collected on a personal basis by reporting to the German Childhood Cancer Registry and the KRANIOPHARYNGEOM Registry 2019 after consent of guardians and, if applicable, patients. Prospective data collection is then performed pseudonymously at the study center in an access database via paper-based CRFs completed at the participating study centers. The central data set for each patient includes patient demographics, diagnosis, type of sellar tumor, and treatment data. Within the KRANIOPHARYNGEOM Registry 2019 enrollment, informed consent is obtained for the collection, storage, and use of biomaterials ("biobanking") for the purpose of reference evaluation and scientific study of the molecular and biological characteristics of sellar tumors.
Registry coordinators are responsible for maintaining sufficient information (name, date of birth, internal clinic number, patient identification number, gender, informed consent) for each patient to identify the patient. According to ICH-GCP guidelines, these documents (patient identification list) must be archived for at least 15 years. Data and biomaterial will be stored for 30 years from date of consent.

Incentives of participation in the registry are to share epidemiological and clinical relevant data for scientific investigations to improve future patient care.

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.

13. Potential benefits and risks of registry participation

Participation in the registry does not result in a direct personal benefit for the patient, but in other benefits due to the gain of scientific knowledge about craniopharyngioma, xanthogranuloma, cysts of Rathke's pouch, meningioma, pituitary adenoma, arachnoid cysts in childhood and adolescence.

The data collection of the routine care does not cause any burdens or risks for the participants. When answering questionnaires, psychological stress may arise if patients/guardians are confronted with their own illness (of the child) as a result of the questions. This risk is to be assessed as very low, since parameters are also queried within usual care. In the unlikely event of exposure to patient assessments, participation can be terminated at any time without any resulting disadvantages. Patients and guardians will be informed of the possibility of terminating registry participation at inclusion and for re-contact. This will ensure that patients and guardians who have experienced psychosocial stress as a result of register participation can refuse to be contacted again.

14. Withdrawal of the registry

Withdrawal from the registry is possible at any time or required if one of the termination criteria is present. The following reasons might lead to individual withdrawal from the registry:

- Withdrawal of consent by legal guardians and/or the patient
- Personal with of the legal guardian and/or the patient
- Unwillingness to participate
- Significant protocol violations (e.g., intentional misreporting)
- Loss of contact

Termination criteria for the registry itself:

- none defined

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