Approximately 40 new cases of craniopharyngioma in children and adolescents are diagnosed in Germany each year. The diagnosis is often made late, sometimes years after the initial appearance of symptoms. Craniopharyngioma is a low-grade malignant tumor with a high survival rate, but because of its anatomical proximity to the optic nerve, pituitary gland, and hypothalamus it often has long-term sequelae that severely impair patients’ quality of life (1). An improvement in its prognosis will require earlier diagnosis and the development of improved neurosurgical and radiotherapeutic treatment strategies in a multidisciplinary approach. Recent multicenter cooperation in this area has led to beneficial results.

**Epidemiology and pathology**
Craniopharyngioma is a non-glial intracranial tumor derived from a malformation of embryonal tissue. Its incidence is 0.5 to 2 cases per million persons per year (106 per year in Germany). 30 to 50 % of all cases become apparent in childhood and adolescence (1). Craniopharyngioma represents 1.2 to 4 % of all childhood intracranial tumors. In childhood and adolescence, its histological type is usually adamantinous, with cyst formation; it also arises in adulthood, with peak incidence between the ages of 50 and 75, most often with a papillary histological type. Cases of craniopharyngioma are systematically documented by the German Pediatric Cancer Registry (Deutsches Kinderkrebsregister) in accordance with international guidelines (2). The degree of case capture by this registry is not yet high enough, however, to permit the calculation of valid incidence figures. From 1980 to 2001, data were obtained on 385 patients in whom a craniopharyngioma was diagnosed at age = 18 years. 345 of the patients were younger than 15 years of age at the time of diagnosis. In the latter group, the sex ratio was 1:1 and the median age at diagnosis was 8 years and 3 months. The survival rate was 93% at 3 years, 91% at 5 years, and 87% at 10 years from the time of diagnosis. Patients who developed the disease in the 1980’s had a lower survival rate than those diagnosed in the 1990’s (survival at 5 years, 88% vs. 96%; p<0.05) (1).

**Clinical manifestations**
The clinical picture at the time of diagnosis is often dominated by non-specific manifestations of intracranial hypertension, such as headache and vomiting in the morning on an empty
stomach ("dry heaves"). Further leading manifestations include visual impairment (62% to 84%) and endocrine deficits (52% to 87%). The latter involve the hypothalamic-pituitary axis and affect the secretion of growth hormone (75%), gonadotropins (40%), adrenocorticotropic hormone (ACTH) (25%), and thyroid-stimulating hormone (TSH) (25%). Neurohormonal diabetes insipidus is present preoperatively in 17% of patients. A study of the history of craniopharyngioma patients before diagnosis (Figure 1) reveals that the initial manifestations often occur long before the diagnosis is made (1). An analysis of anthropometric data obtained in routine checkups before the diagnosis of craniopharyngioma in 90 children (3) revealed that a pathological rate of growth is already demonstrable at age 12 months as an early manifestation of the disease. An increase in weight, in contrast, tends to occur as a later manifestation, shortly before diagnosis (Figure 2). The clinical combination of headache, visual impairment, deficient growth, and polydipsia/polyuria should arouse suspicion of craniopharyngioma in the differential diagnosis (1).

Imaging studies
Both computerized tomography (CT) and magnetic resonance imaging (MRI) reveal craniopharyngioma as a usually cystic tumor of the intra- and/or suprasellar region. CT may be better at revealing calcification, which is found in approximately 90% of tumors. The signal intensity of craniopharyngioma in MRI is highly variable, as it depends on the protein content of the cysts. Solid tumor portions and cyst membranes appear isointense in T1-weighted images, often with a mildly heterogeneous structure. The most common localization is suprasellar, with an intrasellar portion. 20% of tumors are exclusively suprasellar, 5% exclusively intrasellar (4). The combination of solid, cystic, and calcified tumor components is an important radiological clue to the diagnosis (Illustration).

Operative treatment
Before surgery, a tumor-related disturbance of cerebrospinal fluid flow often causes hydrocephalus, which can be of varying severity. The resection of the tumor is the treatment of first choice for restoration of normal CSF flow, but a shunt operation may also be required. For a craniopharyngioma with a large cyst, particularly in infancy or early childhood, a further valuable treatment option is the stereotactic or open implantation of an intracystic catheter, both for the relief of pressure and, in some cases, for the instillation of sclerosing substances.

In children with craniopharyngioma, the stereotactic or open surgical implantation of an intracystic catheter with a subcutaneous reservoir can be a useful means of reducing the volume of the cyst to prolong the interval until radiotherapy or surgical resection. In particular, for patients with large cysts exerting mass effect and, in consequence, marked preoperative visual impairment, a two-staged approach has been proposed, with cyst drainage to relieve pressure and improve vision, followed by resection (5). The operative...
approach is generally dictated by the localization and extent of the craniopharyngioma. A right frontotemporal approach is standard, but purely intrasellar tumors can be operated on by the transsphenoidal route. Tumors arising in childhood usually extend intracranially and must be removed through a transcranial approach. For topographical-anatomical reasons, transsphenoidal surgery has the advantage of not disturbing hypothalamic function (6).

For favorably localized tumors, the treatment of first choice is an attempt at complete microsurgical resection with preservation of visual, hypothalamic, and pituitary function.
(5). For unfavorably localized tumors, there is controversy over whether this should still be attempted or whether a planned limited resection (biopsy, partial/subtotal resection) should be performed instead. Many authors take a critical view of planned radical resection because of the risk of surgically induced deficits (mainly hypothalamic) and the high rate of recurrence (23%) in infants and small children despite complete resection (5). After subtotal resection, the tumor remnant continues to grow in 71% of patients. The rate of progression after subtotal resection followed by radiotherapy is 21% (7, 8). If the tumor progresses after incomplete resection and radiotherapy, scarring may make reoperation more difficult than it would have been if radiation therapy had not been performed. Ultimately, whatever the preoperative intention, the final decision regarding the extent of the surgical resection can only be made intraoperatively by the neurosurgeon.

The data in the published literature to date have not eliminated controversy over the best treatment strategy for craniopharyngioma in childhood and adolescence (intended primary radical resection, versus biopsy/partial resection followed by radiotherapy). At present, there is no clear way to make a well-founded determination of the optimal strategy because of the lack of prospectively acquired data. “Kraniopharyngeom 2000” (11) is a currently ongoing, multicenter, prospective observational study of children and adolescents in Germany with craniopharyngioma that is intended to help answer this question.

Illustration: Development of obesity and localization of craniopharyngioma. Postoperatively, both patients had panhypopituitarism. The patient seen in (a) had a small tumor revealed by MRI (d), which was removed transsphenoidally. Postoperatively, she continued to have normal eating behavior, and her weight developed normally. The patient whose preoperative MRI (b) showed a large tumor extending to the suprasellar region and infiltrating the hypothalamus went on to develop an eating disorder and, consequently, obesity (c). (Modified from Müller HL, Kaatsch P, Warmuth-Metz M, Flentje M, Sörensen N: Kraniopharyngeom im Kindes- und Jugendalter – Diagnostische und therapeutische Strategien. Monatschr Kinderheilkd 2003; 151:1056-63, with the kind permission of Springer Verlag.)
Any discussion of this issue must take account of the late sequelae and quality of life experienced by the patients after treatment. A follow-up study of children whose craniopharyngiomas had been radically microsurgically resected revealed that their quality of life depended to a statistically significant extent on the experience of the operating neurosurgeon (9). The author conducted a multicenter cross-sectional study on the functional capacities of children and adolescents after treatment for craniopharyngioma using the Münster-Heidelberg Skills Rating Scale ("Fertigkeitenskala Münster-Heidelberg," FMH) (10). This study revealed no significant dependence of functional capacities on the intended or achieved degree of resection (Table 1).

### Radiation therapy

Recommendations for the radiation therapy of craniopharyngiomas, derived from the clinical experience of the last few decades (11, 12), are listed in Table 2. Optimal techniques must be used. The target volume must be defined according to the finding of macroscopically visible tumor in the CT and/or MRI images. The resolution of current medical imaging techniques permits the use of a small safety margin, which may be no greater than 5 mm, depending on the precise configuration of the tumor. A smaller safety margin may be chosen in the vicinity of important structures, such as the optic chiasm, as long as the less than perfect precision of radiological localization as well as possible difficulties in the interpretation of images, of both physical and medical nature, are taken into account. A larger safety margin is required if the hypothalamus is involved, even when MRI-based planning is used. Three-dimensional planning and multifield techniques with individual field configurations (collimation) should be used to protect radiosensitive structures and to provide a maximal dose fall-off between the tumor and the adjacent normal structures.

Only limited experience has been gained to date with stereotactic gamma-radiotherapy (Gamma Knife) in the treatment of primary or recurrent craniopharyngioma. For reasons relating to radiation biology, single-dose convergence irradiation seems to be of little value in the treatment of craniopharyngiomas. Another experimental treatment option, the stereotactic instillation of radioisotopes, is mainly applicable to monocular recurrences of craniopharyngioma. This method can only be used for cystic tumors and should only be considered for tumors that recur after both surgery and percutaneous radiation therapy.

---

### Table 1

<table>
<thead>
<tr>
<th>Table 1: Functional capacity as a function of the intended and achieved extent of surgical resection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intended extent</strong></td>
</tr>
<tr>
<td><strong>of resection</strong></td>
</tr>
<tr>
<td><strong>Radical</strong></td>
</tr>
<tr>
<td>Patients</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Radiation</td>
</tr>
<tr>
<td>Age at diagnosis</td>
</tr>
<tr>
<td>Age at last visit</td>
</tr>
<tr>
<td>BMI at last visit</td>
</tr>
<tr>
<td>FMH score at last visit</td>
</tr>
</tbody>
</table>

1Functional capacity measured on the Münster-Heidelberg Skills Rating Scale (FMH) (10).
2The BMI is given as a standard deviation score as described by Rolland-Cachera et al. (24).

Data on the intended extent of resection were available in 135 cases (98%). Significant findings are indicated here, according to degree of significance, by the superscript * for p < 0.01.

Ranges are given in parentheses.

Treatment in case of recurrence or progression of a residual tumor or cyst

The site and rate of progression of the tumor, as well as the patient's age, are important considerations for the decision whether reoperation and/or radiotherapy should be performed. The implantation of an intracystic catheter with a subcutaneous reservoir affords the possibility of repeated decompression of the cyst and often relieves pressure only transiently. The radical resection of a recurrent craniopharyngioma can be rendered more difficult by local postoperative changes from the first operation that make the tumor less easily separable from the adjacent vessels, nerves, and brain tissue. The instillation of sclerosing substances such as bleomycin through an intracystic catheter implanted by a stereotactic or open procedure is a useful method of treatment mainly for cystic recurrent tumors whose anatomical configuration makes them difficult to resect.

Late sequelae and quality of life

Ophthalmological findings

In a French case series (5), 42% of patients were visually impaired at the time of diagnosis of craniopharyngioma; the impairment was moderate in 17% and severe in 25%. Ophthalmoscopy at the time of diagnosis reveals papillary atrophy in 35% to 45% of cases and papilledema somewhat less frequently, in 20% to 35% of cases. According to a meta-analysis of 23 published series, the visual fields were impaired (bitemporal hemianopsia) in 36% of patients at the time of diagnosis. Vision was normal in 30% of patients (5). Visual acuity improved postoperatively in 66% of patients with preoperative visual impairment treated with complete resection and in 46% of those treated with subtotal resection of the tumor.

Neuropsychological deficits

Hypothalamic lesions are associated with emotional lability, rage attacks, abnormal sexual behavior, and deficits of memory and intellectual capacities. Figures found in the literature on the intelligence quotient (IQ) of persons operated on in adulthood for craniopharyngioma are mostly normal. A number of studies of children with craniopharyngioma, however, have revealed disturbances of memory, attention, impulse control, motivation, and socialization resulting from tumor infiltration into the hypothalamus. Longitudinal studies on the development of functional capacities in craniopharyngioma patients have revealed marked deficits as a function of tumor size and hypothalamic involvement (13, 14).

Endocrine deficits

Most patients (85% to 95%) suffer from multiple deficits of hypothalamic-pituitary function, ranging to panhypopituitarism, in the first few days after surgery regardless of the extent of...
A full restoration of preoperatively deficient hormonal function occurs after craniopharyngioma resection only in exceptional cases (15). Irreversible diabetes insipidus follows 80% to 93% of all complete microsurgical resections (9), and growth hormone deficiency occurs in 75% of cases. The safety and effectiveness of substitution therapy with recombinant growth hormone is well documented.

Obesity and eating disorders

Obesity and eating disorders are observed in 40% to 50% of craniopharyngioma patients (16). A disturbance of hypothalamic structures, particularly the ventromedial hypothalamus, by the tumor is considered to be the major pathogenetic factor for hyperphagia and obesity. De Vile et al. (17) assessed the extent of hypothalamic involvement with the aid of imaging studies. The body mass index (BMI) of the affected patients was positively correlated with the degree of hypothalamic damage.

Roth et al. (18) measured serum leptin levels in craniopharyngioma patients and found significantly elevated leptin concentrations, in relation to BMI, in patients with a suprasellar tumor component. They proposed that the normal inhibition of appetite fails to occur because of disruption of the negative feedback loop in which leptin, formed in adipocytes, binds to hypothalamic leptin receptors. Accelerometric measurements show that craniopharyngioma patients have a markedly lower than normal level of physical activity in relation to their caloric intake (19). Marked daytime fatigue and disturbances of the day-night rhythm have been demonstrated in obese craniopharyngioma patients (20). Daytime fatigue and obesity in these patients were both correlated with low nocturnal melatonin levels; the proposed pathogenetic mechanism involves impaired hypothalamic regulation of melatonin rhythmicity in patients with suprasellar craniopharyngioma. Lustig et al. (21) postulated hypothalamic disinhibition of vagal output as a cause of increased beta-cell stimulation, leading to hyperinsulinism and obesity. In a randomized, double-blinded study, however, treatment with a somatostatin analog (octreotide) to suppress beta-cell activity resulted in only a moderate reduction of weight (21).

Despite the availability of these promising therapeutic approaches, it must be emphasized that there is currently no generally accepted pharmacological therapy for obesity in children and adolescents with craniopharyngioma that has been shown to be effective in controlled studies.
Quality of life
No prospective studies have yet been published on the quality of life of patients who underwent treatment for craniopharyngioma in childhood and adolescence. A retrospective study of functional capacity using the FMH found significantly lower percentile rankings for such patients than for age-matched controls (22). The FMH quantifies the ability to perform everyday psychomotor tasks. The patients’ marked obesity was responsible for their low self-rating of their functional capacity.

The state of studies in the field
There are no randomized, controlled studies on the treatment of craniopharyngioma. Reports in the literature mainly refer to single-center, heterogeneous groups of patients that were analyzed retrospectively. A brief summary of interdisciplinary guidelines on the treatment of craniopharyngioma in childhood and adolescence (12) can be found on the Internet at www.avmf.org.

Perspectives
Because craniopharyngioma is a rare disease, children and adolescents who have it should be documented uniformly in a nationwide prospective study. "Kraniopharyngeom 2000" (11) was designed as an observational study within the treatment network of the German working group for brain tumor studies (Hirntumorstudien, HIT). In this study, data are collected on the treatments provided and on the postoperative outcome. From May 2001 to September 2005, 88 newly reported patients were entered into the prospective evaluation. An interim calculation of event-free survival rates reveals frequent early events (i.e., tumor progression) after subtotal resection and recurrent tumors after complete resection in the first three years after primary surgery (Figure 3). A high rate of early events after treatment (tumor progression in five patients - three cystic, two solid) was also seen in the subgroup of patients who were treated with radiation (n = 16) (Figure 3b). Long-term results will be obtained after further observation.

Acknowledgement
Supported by the German Pediatric Cancer Foundation (Deutsche Kinderkrebsstiftung), Bonn (www.kinderkrebsstiftung.de). The authors express particular thanks to Mrs. Ursel Gebhart for her help in the writing of the manuscript.

Conflict of Interest Statement
The authors declare that no conflict of interest exists according to the Guidelines of the International Committee of Medical Journal Editors.

Manuscript received on 10 January 2006, final version accepted on 21 February 2006.

Translated from the original German by Ethan Taub, M. D.

REFERENCES


Corresponding author
PD Dr. med. Hermann L. Müller
Klinik für Allgemeine Kinderheilkunde, Hämatologie/Onkologie
Zentrum für Kinder- und Jugendmedizin
Klinikum Oldenburg gGmbH
Dr.-Eden-Str. 10, 26133 Oldenburg, Germany
mueller.hermann@klinikum-oldenburg.de

This text is a translation from the original German which should be used for referencing. The German version is authoritative.