Craniopharyngioma

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This report is a review of findings on the diagnosis, treatment, clinical course, and prognosis of craniopharyngioma patients. Craniopharyngiomas are rare, partly cystic and calcified embryonic malformations of the sellar/parasellar region with low histological grade (WHO I°). A bimodal age distribution has been shown, with peak incidence rates in childhood-onset at 5–14 years and adult-onset craniopharyngioma at 50–74 years. Clinical manifestations are related to hypothalamic/pituitary deficiencies, visual impairment, and increased intracranial pressure. If the tumor is favorably localized, the therapy of choice is complete resection, with care taken to preserve optical and hypothalamic functions. In patients with unfavorable tumor localization (ie, hypothalamic involvement), recommended therapy is a limited hypothalamus-sparing surgical strategy followed by local irradiation. Although overall survival rates are high (92%), recurrences and progressions are frequent. Irradiation has proven effective in reducing recurrences and progression, and timing of postsurgical irradiation in childhood-onset cases is currently under investigation in a randomized multinational trial (KRANIOPHARYNGEOM 2007). Anatomical involvement and/or surgical lesions of posterior hypothalamic areas can result in serious quality of life-compromising sequelae such as hypothalamic obesity, psychopathological symptoms, and/or cognitive problems. It is crucial that craniopharyngioma be managed as a frequently chronic disease, providing ongoing care of pediatric and adult patients' clinical and quality of life consequences by experienced multidisciplinary teams. **(*Endocrine Reviews* 35: 513–543, 2014)**

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I. Introduction

Craniopharyngiomas are rare embryonic malformations of the sellar and parasellar area with low histological grade (WHO I°). Despite high survival rates (87 to 95% 20-y overall survival in childhood-onset craniopharyngioma), quality of life is frequently impaired in long-term survivors due to sequelae caused by the anatomical proximity of the tumor to the optic nerve/chiasma and hypothalamic–pituitary axes (1–6). Adult-onset craniopharyngioma patients have much higher mortality compared to the general population, namely an up to 19-fold higher cerebrovascular mortality (7, 8). Any clinically significant improvement in the prognosis of craniopharyngioma patients will require the development of risk-adapted neurosurgical and radio-oncological treatment strategies in a multidisciplinary setting that provides medical as well as psychosocial support for these patients (6, 9, 10). Due to the rareness of the disease, high survival rates, and persistent adverse quality of life effects, recent

Abbreviations: BMI, body mass index; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging.

multicenter cooperation has already led to beneficial results (2, 11).

II. History

In 1840, von Mohr described the rapid development of obesity in a case of a pituitary tumor (12). Zenker in 1857 was the first to identify masses of cells resembling squamous epithelium along the pars tuberalis and pars distalis of the pituitary (13). Extensive study by Luschka (14) of the squamous epithelial cells in the adenohypophysis followed in 1860. In 1902, Saxer (15) reported a tumor consisting of these cells. Two years later, Erdheim (16), after a systematic study of the squamous epithelial cells in the adenohypophysis, described them as occurring in the glands of adult patients, usually on the anterior surface of the infundibulum and in groups or islets of variable size, shape, and number. Because a few groups of these cells contained small cysts similar to some pituitary tumors unnamed at that time, he was convinced that both lesions had the same origin and called them hypophyseal duct neoplasms. Interestingly, he did not find any cell rests along the route of the regressed craniopharyngeal duct, a discrepancy explained by von Mihalkovitc's theory that the developing adenohypophysis underwent a forward and upward rotation, carrying with it the cranial insertion of the gland. In 1932, squamous epithelial cells were detected in the pituitary glands of childhood populations—in this instance by Susman (17). The first attempt at surgical removal of such a tumor was reported in 1910 by Lewis (18). During the following years, different terminologies were used, until 1932 when the name "craniopharyngioma" was introduced by Cushing (19).

III. Epidemiology

Craniopharyngioma is quite rare, with an incidence of 0.5 to 2 cases per million persons per year, 30 to 50% of all cases presenting during childhood and adolescence (20, 21). Craniopharyngioma represents 1.2 to 4% of all childhood intracranial tumors (22–24). In childhood and adolescence, its histological type is usually adamantinomatous with cyst formation (25–27). Craniopharyngioma can be detected at any age, even in the prenatal and neonatal periods (25, 28). A bimodal age distribution has been shown, with peak incidence rates in children of ages 5 to 14 years and adults of ages 50 to 74 years (21). In population-based studies, no gender differences have been observed (29, 30). Craniopharyngioma cases have been reported within two families (31, 32), but an underlying genetic susceptibility has not been verified.

The German Pediatric Cancer Registry systematically documents cases of childhood craniopharyngioma (33). Their data from 1980 to 2007 obtained for 496 childhood craniopharyngioma patients diagnosed at ≤18 years of age reveal that most patients (n = 451; 91%) were younger than 15 years of age at the time of diagnosis, with a 1:1 sex ratio and a median age at diagnosis of 8.8 years. The 1980 to 2007 (contemporary) survival rate is 97% after 3 years from diagnosis, 96% after 5 years, and 93% after 10 years. Patients who developed the disease in the 1980s had a lower survival rate than those diagnosed in the 1990s (survival at 5 years, 91% vs 98%, respectively) (31, 34).

IV. Pathology

There are two craniopharyngioma subtypes: adamantinomatous and papillary. Adamantinomatous craniopharyngioma is recognized by the presence of squamous epithelium disposed in cords, nodules, and irregular trabeculae bordered by palisaded columnar epithelium. These islands of densely packed cells merge with loosely cohesive aggregates of squamous cells known as stellate reticulum (Figure 1A). Nodules of "wet keratin" representing remnants of pale nuclei embedded within an eosinophilic keratinous mass are found in either the compact or looser areas. Cystic cavities containing squamous debris are lined by flattened epithelium. Granulomatous inflammation associated with cholesterol clefts and giant cells may be detectable, but this is more typical for xanthogranuloma. Piloid gliosis with abundant Rosenthal fibers is often seen at the infiltrative interface of the tumor and should not be mistaken for pilocytic astrocytoma. The question of "malignant transformation" of craniopharyngioma has been raised in the literature, but this appears to be very rare (25).

Three essential features of the second subtype—papillary craniopharyngioma—include a monomorphous mass of well-differentiated squamous epithelium lacking surface maturation, the picket fence-like palisades and wet keratin. As noted, another contrasting point is the absence of calcification. Only rarely are ciliated epithelium and goblet cells encountered (25).

Multiple chromosomal abnormalities have been reported in two cases by classic cytogenetic analysis; both tumors had abnormalities involving chromosomes 2 and 12 (35, 36). More than 70% of adamantinomatous craniopharyngiomas harbor a mutation of the β-catenin gene (Figure 1B) (37–40). Most of the mutations affect exon 3, which encodes the degradation targeting box of β-catenin compatible with an accumulation of nuclear β-catenin protein (37). In a few

Figure 1.

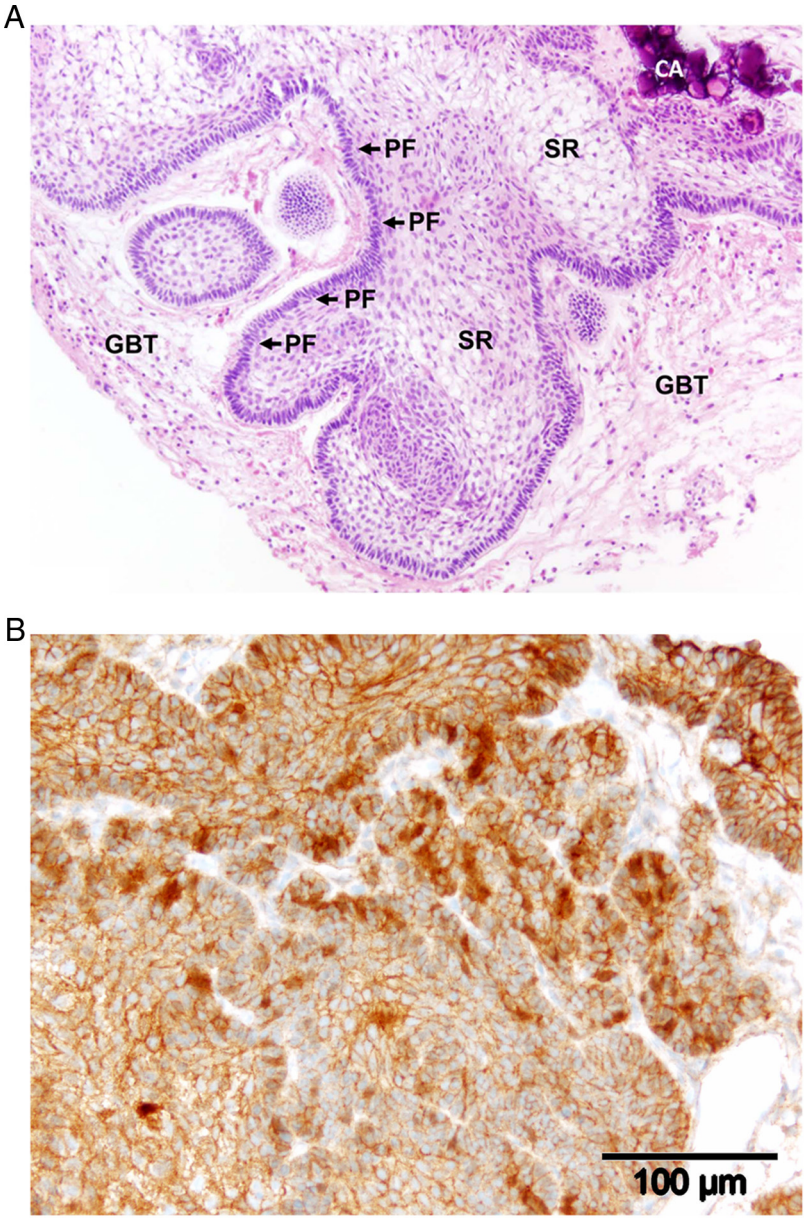

Figure 1. Histology. A, Adamantinomatous craniopharyngioma with typical dense, picket fence-like basal layer areas with more loose texture of the squamous epithelium (stellate reticulum) and calcifications (upper right corner). Protrusions of the epithelial tumor into the gliotic brain tissue can be seen. Hematoxylin and eosin staining. CA, calcification; PF, picket-fence; SR, stellate reticulum; GBT, gliotic brain tissue. [Modified from H. L. Müller et al: Xanthogranuloma, Rathke's cyst, and childhood craniopharyngioma: results of prospective multinational studies of children and adolescents with rare sellar malformations. *J Clin Endocrinol Metab*. 2012;97:3935–3943 (77), with permission. © The Endocrine Society.] B, β-Catenin immunohistochemical staining of an adamantinomatous craniopharyngioma showing the nuclear staining pattern (courtesy of T. Pietsch, Bonn, Germany).

cases of adamantinomatous craniopharyngioma, the same β-catenin mutations occurring in the epithelial cells have been identified in mesenchymal cells. Such observations suggest a biphasic nature of a subgroup of adamantinomatous craniopharyngiomas (40). In contrast, no mutations have been demonstrated in papillary craniopharyngioma. Comparative genomic hybridization studies on two large series of craniopharyngiomas have failed to show significant chromosomal imbalances in adamantinomatous and papillary craniopharyngioma (41, 42). Another comparative genomic hybridization study in nine adamantinomatous craniopharyngiomas revealed at least one genomic alteration in 67% of the studied cases (43).

V. Pathogenesis

Craniopharyngioma is a nonglial intracranial tumor derived from a malformation of embryonic tissue (44). There are differing hypotheses on its embryonic origin: originating from ectodermal remnants of Rathke's pouch vs originating from residual embryonal epithelium of the anterior pituitary gland and of the anterior infundibulum (44). Pathogenesis of craniopharyngioma, although not completely understood (5, 44–47), is explained by two theories: embryonic and metaplastic.

A. Embryonic

Adamantinomatous craniopharyngiomas arise from neoplastic transformation of embryonic squamous cell nests of the involuted craniopharyngeal duct that initially connects Rathke's pouch with the stomodeum. During the process of proliferation and rotation of the cells of Rathke's pouch leading to the formation of the adenohypophysis, cell remnants of the craniopharyngeal duct are spread through the intrasellar and suprasellar region. The rotation of the adenohypophysis is caused by different rates of cellular multiplication, resulting in a spread of cells of the craniopharyngeal duct to the suprasellar region, which is the most frequent location of craniopharyngiomas. The rare location at the cerebellopontine angle could fit with this hypothesis (46, 48).

B. Metaplastic

Papillary craniopharyngiomas are the result of metaplasia of the adenohypophyseal cells in the pars tuberalis of the adenohypophysis, resulting in the formation of squamous cell nests. This theory is supported by the presence of metaplastic nests in the gland (increasing with age) and of hormones contained in the squamous nests. One case of a papillary craniopharyngioma has been described with features suggesting metaplasia from remnants of a Rathke's cleft cyst (47).

Recent observations have given insight into biological markers of pituitary tumors (37–39, 49, 50). β-Catenin expression has been studied by immunohistochemical techniques in adamantinomatous craniopharyngioma, papillary craniopharyngioma, Rathke's cyst, odontogenic cysts, pituitary adenomas, and pilomatricoma—a benign skin tumor. The pattern of β-catenin immunostaining (Figure 1B) has been found to be similar in adamantinomatous craniopharyngiomas, pilomatricoma, and calcifying odontogenic cysts, but different from Rathke's cysts, papillary craniopharyngioma, and pituitary adenoma in which β-catenin accumulation is absent (39, 50, 51). This protein has been identified as a downstream component of the Wnt signal transduction pathway that regulates cellular proliferation, morphology, and development (38). The mutations of genes encoding β-catenin (*CTNNB1* and *APC*) are an exclusive characteristic of adamantinomatous craniopharyngioma, and they likely play a role in its initiation and growth (38). Kato et al (38) discussed the similarity in genetic patterns between pilomatricoma, calcifying odontogenic cysts, and adamantinomatous craniopharyngioma regarding the role of reactivation of the Wnt pathway in determining the tumor origin in the remnants of Rathke's pouch. Because novel treatment strategies (antiestrogens, anti-inflammatory drugs) have been considered for neoplasm (desmoid tumors) with Wnt signal abnormalities (38), these authors postulate a possible application of such innovative therapies to these pathologies.

Dattani et al (52, 53) generated a unique mouse model for adamantinomatous craniopharyngioma by expressing a degradation-resistant mutant form of β-catenin (encoded by the *Ctnnb1* gene) that leads to the overactivation of the Wnt pathway in the developing pituitary gland. Their research demonstrated a causative effect of mutant β-catenin in the etiology of human adamantinomatous craniopharyngioma, confirming previous studies that identified activating *CTNNB1* mutations in samples of human adamantinomatous craniopharyngioma (37, 38, 40). The similarities in the pathogenesis between the mouse and human tumors are significant. For instance, immunohistochemistry on mouse and human tumors shows clusters of cells with nucleocytoplasmic accumulation of β-catenin surrounded by cells exhibiting normal membranous staining (52). Using genetic approaches in the mouse, the authors were able to isolate the cluster cells from the rest of the tumor and perform a gene profiling study. This revealed several genes and pathways that were differentially expressed in these two cell compartments in the murine model (54). Of particular clinical relevance, the authors demonstrated that many of these genes/pathways were also differentially expressed in human adamantinomatous craniopharyngioma, further enforcing the adamantinomatous craniopharyngioma mouse model as a useful genetic tool to investigate the pathogenesis of craniopharyngioma in order to identify possible molecular targets for chemical treatments.

VI. Location

Craniopharyngiomas can arise anywhere along the craniopharyngeal canal, but most of them occur in the sellar/parasellar region. The majority (94–95%) has a suprasellar component (purely suprasellar, 20–41%; both supra- and intrasellar, 53–75%) (55–57), whereas the purely intrasellar ones represent the least common variety (5–6%) (56, 57). Occasionally, a suprasellar tumor extends into the anterior (9%), middle (8%), or posterior (12%) fossa (40). Other rare locations include the nasopharynx (58), paranasal area (59), sphenoid bone (60), ethmoid sinus (61), intrachiasmatic area (62), temporal lobe (63), pineal gland (64), posterior cranial fossa (65), cerebellopontine angle (66), midportion of the midbrain (67), or completely within the third ventricle (68).

VII. Presenting Clinical Manifestations

The diagnosis of childhood craniopharyngioma is often made late—sometimes years after the initial appearance of symptoms (31)—with a clinical picture at the time of diagnosis often dominated by nonspecific manifestations of intracranial pressure (eg, headache and nausea). Further primary manifestations are visual impairment (62–84%) and endocrine deficits (52–87%). Among adult-onset craniopharyngioma patients, hormonal deficits at the time of diagnosis are much more pronounced when compared with childhood-onset craniopharyngioma patients. Endocrine deficits are frequently caused by disturbances to the hypothalamic–pituitary axes that affect GH secretion (75%), gonadotropins (40%), ACTH (25%), and TSH (25%). At the time of diagnosis, 40 to 87% of patients present with at least one hormonal deficit (4, 69, 70), and other endocrine symptoms such as neurohormonal diabetes insipidus are present preoperatively in 17 to 27% of

Figure 2.

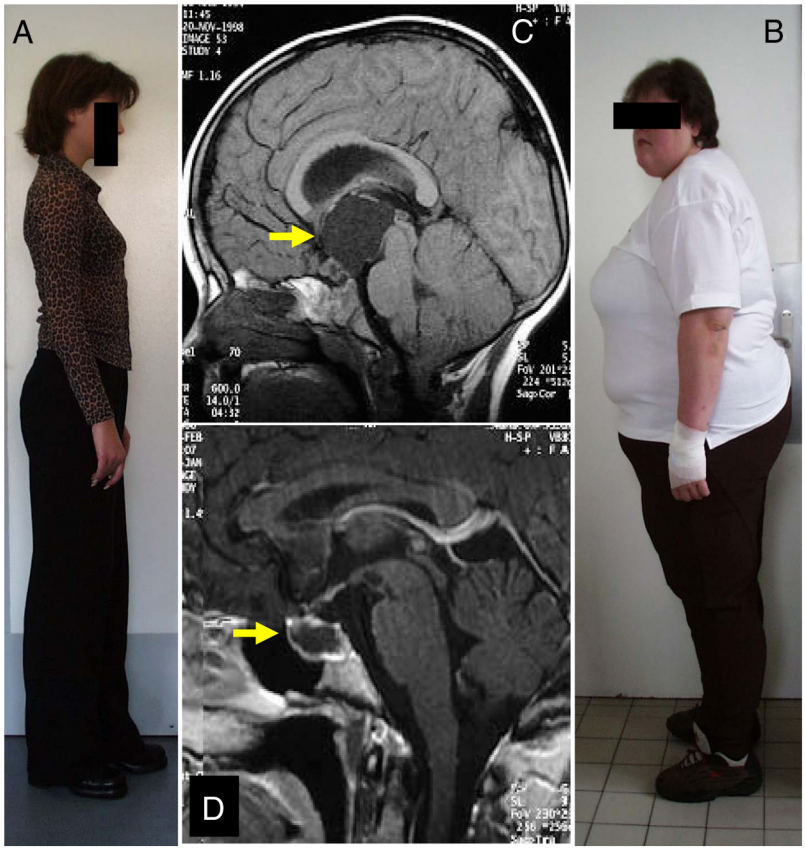

Figure 2. Degree of obesity in relation to location of craniopharyngioma. In both patients, craniopharyngioma (indicated by arrow on MRI before surgery) could be completely resected. Both patients had complete hypopituitarism after surgery requiring endocrine substitution of all hypothalamic–pituitary axes. The patient depicted in panel B developed severe obesity due to hypothalamic lesions of suprasellar parts of the craniopharyngioma (C). The patient depicted in panel A presented with a small tumor confined to the sellar region (D). After complete resection, she maintained normal weight without any eating disorders. [Modified from H. L. Müller et al: Childhood craniopharyngioma - diagnostic and therapeutic strategies. *Monatsschr Kinderheilkd*. 2003;151:1056–1063 (33), with permission. © Springer-Verlag.]

patients (4, 70, 71). An analysis of anthropometric data obtained in routine checkups before the diagnosis of childhood craniopharyngioma in 90 children (72) revealed that a pathologically reduced growth rate—an early manifestation of the disease—presents in patients as young as 12 months, but that significant weight gain, predictive of hypothalamic obesity, tends to occur as a later manifestation, shortly before diagnosis. The recent literature has documented that any clinical combination of headache, visual impairment, decreased growth rate, and/or polydipsia/polyuria should arouse suspicion of childhood craniopharyngioma in the differential diagnosis process (2).

VIII. Imaging Studies

Both computerized tomography 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%) are exclusively intrasellar (73–76). Computerized tomography 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 (Figure 2). 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 includes hypothalamic glioma and optic glioma, Langerhans cell histiocytosis, Rathke's cleft cyst, xanthogranuloma, intracranial germinoma, epidermoid tumor, thrombosis of arachnoid cysts, colloidal cyst of the third ventricle, pituitary adenoma, an aneurysm, and rare inflammatory variations (73, 77).

MRI before and after gadolinium application is the standard imaging for detection of craniopharyngioma, further imaged by native computerized tomography to detect calcifications (73). After preoperative detection of calcifications and complete resection confirmed by postoperative MRI, a postsurgical native computerized tomography of the sellar/parasellar area (without contrast medium application) is recommended for definitive confirmation of complete resection (73). Imaging for detection of relapse or progression during follow-up should be confined to MRI to increase diagnostic sensitivity and to decrease radiation burden.

IX. Treatment Strategies

A. Neurosurgery

1. Strategies and effects

For favorably localized craniopharyngioma (ie, 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 (78–81). For unfavorably localized tumors too close to or too 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 (2, 81, 82). 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 (83, 84). Recurrences at ectopic localizations are reported (85). Although after 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% (86). Elowe-Gruau et al (87) recently published the results of a single institution study at Necker (Paris, France) showing that a hypothalamus-sparing surgical strategy combined with post-surgical 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 (87).

However, the published literature to date (57, 71, 83, 87–92) has not settled the controversy over the best treatment strategy for craniopharyngioma (intended primary gross total resection, vs 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 quality of life are not clearly characterized based on the retrospective data published to date. A retrospective analysis cited primary therapy full-scale IQ losses of 9.8 points after a single complete resection compared to a loss of 1.25 points after limited resection followed by radiation therapy (92). For a second surgical intervention carried out after 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 (93). 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 (79). After transcortical puncture of the lateral ventricle, the endoscope can be moved inside the inner cerebrospinal fluid (CSF) space through the foramen of Monro within some limits. Besides cyst punctures and biopsies (94), catheters can be placed under optic control.

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 (95, 96). 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 third ventricle can be reached by opening of the lamina terminalis behind the optic chiasm (97). 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 foramen of Monro (98). 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.

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 (99, 100). Several reports of extended approaches to suprasellar craniopharyngiomas have been published (100–102). 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 (102). CSF fistulas are another complication, requiring a meticulous technique to prevent. It is imperative 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 (77, 103, 104). In comparison to transcranial procedures, potential advantages of transsphenoidal approaches include the avoidance of craniotomy

Table 1. Postoperative Radiotherapy in Craniopharyngioma/Conventional Techniques (Tumor Control and Survival)

First Author (Ref.)	No. of Patients (% of Children at Dgx)	PFS, %			OS, %		
		5 y	10 y	20 y	5 y	10 y	20 y
Carmel (116)	14 (100)	78	78	n.a.	90	80	n.a.
Flickinger (118)	21 (43)[b]	95	95	n.a.	89	89	n.a.
Rajan (91)	173 (45)[a]	n.a.	83	n.a.	n.a.	77	n.a.
Hetelekidis (90)	46 (100)[c]	n.a.	86	n.a.	n.a.	91	n.a.
Mark (119)	49 (31)[b]	96	n.a.	n.a.	96	96	n.a.
Habrand (117)	37 (100)[a]	78	56	n.a.	91	65	n.a.
Varlotto (120)	24 (46)[b]	n.a.	89.1	54	n.a.	100	92.3
Pemberton (121)	87 (32)[a]	n.a.	77	66	n.a.	86	76

Abbreviations: PFS, progression-free survival; OS, overall survival; Dgx, diagnosis; n.a., not analyzed.

[a] Considered children <16 years old.

[b] Considered children <18 years old.

[c] Considered children ≤21 years old.

and brain retraction and reduced neurovascular manipulation (105).

B. Irradiation

1. Conventional external radiotherapy

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 toward less infiltrative growth, permitting a small safety margin of 5 mm maximum (106, 107). 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 has been established worldwide (86, 92, 106–115).

An excellent long-term outcome of conventional radiotherapy was found in many retrospective series (90, 91, 116–121) reporting 10- and 20-year progression-free survival up to 95 and 54%, respectively (Table 1). Advances in radiotherapeutic technologies have opened up new approaches in the radio-oncological management of craniopharyngioma (Table 2). Selection of the adequate treatment technology is a cause of ongoing debate. The 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 (122–126). Stereotactic irradiation can be given in a single dose as stereotactic radiosurgery or in multiple doses as fractionated stereotactic radiotherapy. The modern systems permit an exact calculation of dose distribution within the tumor and provide a steeper dose gradient to surrounding normal tissue. If a cystic component is present, careful monitoring during radiotherapy is necessary because changes and even enlargements in cystic volume are possible during irradiation (127).

2. Proton beam therapy

Proton beams have an "inverse dose profile" across the tissues, whereby the dose released by the particles in-

Table 2. Results After Modern External Fractionated Radiotherapy Techniques

First Author (Ref.)	No. of Patients (% of Children at Dgx)	Technique	Dose, Gy	PFS, %	OS, %
Selch (126)	16 (31)[c]	3-D CFSR	55 fractionated	75 at 3 y	93 at 3 y
Combs (122)	40 (15)[b]	3-D CFSR	Median, 52.2; range, 50.4–56; single dose 1.8–2	100 local control at 5 and 10 y	79/89 at 5/10 y
Minniti (123)	39 (49)[a]	3-D CFSR	50 in 30–33 fractions	97/92 at 3–5 y	100 at 3/5 y
Hashizume (125)	10 (10)[a]	FSRT Novalis IMRT	30–39 in 10–15 fractions (median, 33)	Control rate, 100	Not reported
Kanesaka (124)	16 (0)	3-D CFSR	30 in 6 fractions	82.4 at 3 y local control	94.1 at 3 y

Abbreviations: PFS, progression-free survival; OS, overall survival, CFSR, conformal stereotactic fractionated radiotherapy; FSRT, fractionated stereotactic conformal radiotherapy; IMRT, intensity-modulated radiation therapy; Dgx, diagnosis; 3-D, three-dimensional.

[a] Considered children <16 years old.

[b] Considered children <18 years old.

[c] Considered children <20 years old.

creases 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 et al (128) published a report on 15 craniopharyngioma patients treated with combined proton-photon irradiation for residual or recurrent disease. Actuarial 5- and 10-year local control rates were 93 and 85%, respectively, with 10-year 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 et al (129) published a preliminary report in 2006 on 16 patients treated with proton beam therapy. Local tumor control was achieved in 14 of 16 (87.5%) patients. During follow-up (12 to 121 mo later), late sequelae included newly diagnosed panhypopituitarism, a cerebrovascular accident, and an out-of-proton-field posterior fossa meningioma (59 mo after proton beam therapy administered to a 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, whereas one patient required cyst drainage during treatment (127).

Clinical outcome data are still very limited for assessing the value of proton beam therapy compared to modern photon therapy because 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 (130–132). As proton beam therapy becomes more available, additional data on this promising therapy are expected.

3. Stereotactic radiotherapy

Stereotactic radiotherapy is a modality combining the accurate focal dose delivery of stereotactic radiosurgery with the radiobiological advantages of fractionation (122). 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 (133–135).

The data on the usefulness of stereotactic radiotherapy for the management of craniopharyngiomas are limited, but the larger series published thus far provide promising results (134, 135). The median target dose reported was 52.2 Gy with conventional fractionation and a safety margin of 2 mm. The 10-year 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 y) follow-ups (7 mo to 12 y) revealed that 16.6% of subjects developed impaired pituitary function; no deterioration of vision, radionecrosis, or second malignancies were observed.

4. Radiosurgery

The most frequently used system for delivery of single fraction radiotherapy is the gamma knife (136). 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 brainstem were 8 to 9 and 12 to 14 Gy, respectively (137–144). 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 (137, 139, 140) (Table 3).

5. Intracavitary β-irradiation

Intracavitary β-irradiation (brachytherapy) is a minimally invasive management strategy, first reported by Leksell in 1867 (145). 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 (146, 147). Subsequent studies assessed the efficacy of various β- and γ-emitting isotopes (mainly ^{32}phosphate, ^{90}yttrium, ^{186}rhenium, and ^{198}gold) (148–155); because none of them has the ideal physical and biological profile (ie, pure β-emitter with short half-life and with tissue penetrance limited to cover only the cyst wall) (154), there is no consensus on which therapeutic agent is the most suitable. ^{90}Yttrium has the shortest physical half-life (2.67 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 (152). ^{32}Phosphate is a pure β-emitting radionuclide but with a long

Table 3. Outcome After Stereotactic Single Dose Radiosurgery in Craniopharyngioma (Gamma Knife)

First Author (Ref.)	No. of Patients (% of Children at Dgx)	Dose, Gy	PFS, %	OS, %
Prasad (141)	9 (33)[a]	13	62.5	n.a.
Mokry (137)	23 (35)[a]	8–9.7 (MD)	74	n.a.
Chung (138)	31 (29)[b]	9.5–16	87	n.a.
Yu (144)	46 (median age, 39 y; range, 3–60 y)	8–18 (MD)	89.5	n.a.
Chiou (142)	10 (70)[c]	Median, 16.4	58	n.a.
Ulfarsson (143)	21 (52)[a]	3–25	34	n.a.
Amendola (139)	14 (71)[b]	14 (11–20)	86	All alive after 6–86 mo follow-up
Kobayashi (140)	100 (38)[a]	11 (MD)	61 and 54, at 5 and 10 y	94.1 and 91 at 5 and 10 y

Abbreviations: PFS, progression-free survival; OS, overall survival; MD, marginal dose; n.a., not analyzed; Dgx, diagnosis.

[a] Considered children <15 years old.

[b] Considered children <16 years old.

[c] Considered children ≤18 years old

half-life (14.3 d) (154). Both ^{186}rhenium and ^{198}gold emit a considerable amount of γ-radiation (152).

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 (86, 156–159). Before 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 (160). A nonrandomized 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 (134) (Table 4).

C. Instillation of sclerosing substances for cystic recurrent 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. Although it usually relieves pressure transiently, it is a useful therapeutic method for cystic recurrent tumors whose anatomical configuration and localization make them difficult to resect (161, 162). 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 (134, 163–169) (Table 4). Severe neurotoxic side effects were observed in some cases due to cystic leakage of bleomycin into CSF (170). Accordingly, a thorough neuroradiological imaging for exclusion of cystic leakage is warranted before instillation of bleomycin.

Intracystic instillation of interferon α was first used by Cavalheiro et al (171, 172), who have published the most experiences in treating cystic childhood craniopharyngiomas. Their latest publication (172) included 60 children with a mean age of 11 years, treated at three different institutions from 2000 to 2009. Twenty-nine of the 60 patients received intracystic interferon α after initial surgery or after bleomycin treatment had failed; the remaining 31 were treated with interferon α as a first-line treatment. Although 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 interferon α, its intracystic instillation is a promising therapeutic option for predominantly monocystic craniopharyngiomas (172–174) (Table 4).

D. Treatment strategies and quality of life

To address the impact of the above treatment strategy issues, a long-term multinational prospective surveillance study of children and adolescents with craniopharyngioma, KRANIOPHARYNGEOM 2000, was conducted (77, 103, 104). Newly diagnosed patients (2001 to 2006) from Germany, Austria, and Switzerland were entered into the prospective evaluation. An analysis of 3-year, event-free survival rates revealed frequent early events (ie, tumor progression after incomplete resection and tumor

Table 4. Intracystic Treatment Modalities in Craniopharyngiomas—Retrospective Reviews Including Children

First Author (Ref.)	No. of Patients (% Children)	Mean Age (Range), y	CR	PR	Mean FU (Range), y	Mean PFS (Range), y	Reported Toxicities and Complications
Isotopes							
Pollock (149)	30 (33)	35 (3–70)	0.10	0.83	3.1 (0.6–9.7)	NR	Three new behavioral problems, visual decline, 3 new onset DI
Voges (150)	62 (52)	17[e] (4–71)	0.45	0.35	11.9[e] (1.5–16.4)	NR	Three amaurosis, 1 visual field cut, 3 endocrine deficits, 1 death 9 mo after treatment
Hasegawa (153)	49 (31)	29 (3–74)	0.17	0.59	4.1	NR	Visual or endocrine deterioration
Derrey (147)	42 (26)	38.7 (5–85)	0.44	0.44	3.6 (0.7–12.3)	NR	Two septic meningitis, 2 chemical meningitis, 1 intracranial hypertension, 2 central hyperthermia, 3 visual acuity or field decline, 1 memory loss
Szeifert (157)	60 (22)	27.7 (3–67)	0.45	0.30	NR	NR	Three visual deterioration, 6 transient CN III palsy, 1 death/ meningoventriculitis 6 wk after intervention, 2 hypothalamic/thalamic vascular injury
Barriger (159)	19 (NR)	20 (3–54)	0.05	0.26	5.2[e] (0.7–11.3)	0.8[e] (0.1–4.5)	Six increased pituitary deficiencies, 1 new field deficit
Bleomycin							
Takahashi (163)[a]	7 (100)	8.4 (2–13)	NR	NR	NR (21–26)	12 (0.1–26)[b]	Transient mild fever
Hader (164)	9 (100)	8.4 (2–14)	0.14	0.71	3 (0.5–5)	NR	Two transient headaches and fever, 1 panhypopituitarism
Mottolese (165)	24 (83)	14.3 (0.2–64)	0.38	0.63	5	5 (2–10)	One blindness (after toxic dose)[c]
Park (166)	10 (50)	30.2 (3–65)	NR	NR	2.8 (1–6.6)	NR	One visual disturbance, 1 cerebellar infarction/death, 1 hypersomnia/ memory impairment, 1 transient mental changes
Mottolese (167)	24 (100)	NR (6–16)	0.50	0.25	6.7 (1–14)	NR	One blindness (after toxic dose)[c]; 3 new onset of DI, 11 endocrine insufficiency, visual deterioration
Takahashi (168)	11 (100)	NR (2–14)	0.27	0.64	NR (3–16)	NR	One hypothalamic--pituitary insufficiency/death during FU
Hukin (169)	17 (100)	6[e] (1–14)	0.29	0.35	5[e] (0.5–10.2)	0.7[e] (0.3–6.1)[d]	Decreased level of consciousness/ panhypopituitarism, 1 multiple CN deficits/hemiparesis
Interferon α							
Cavalheiro (171)	9 (100)	10 (1.8–18)	0.78	0.22	1.8 (1–3.5)	NR	One arthralgia/chronic fatigue/depression
Ierardi (174)	21 (100)	10 (1–19)	0.50	0.50	2.25 (0.5–4)	NR	NR
Cavalheiro (172)	60 (100)	11 (1.6–18)	NR	0.78	3.7 (0.3–7)	NR	Transient headache/ fever/fatigue/ arthritis; 8 new endocrine dysfunction
Bartels (173)	6 (100)	10.8 (4–18)	0.2	0.6	1.4 (0.1–2.5)	NR	Transient headache one nausea[c] vomiting

Abbreviations: DI, diabetes insipidus; NR, not reported; PFS, progression-free survival; CR, complete response; PR, partial response (≥50% shrinkage); FU, follow-up; CN, cranial nerve.

[a] Including follow-up data provided in Takahashi *et al.* (168).

[b] Estimate from authors based on provided data.

[c] Likely same patient.

[d] Refers to 12 patients treated at time of initial diagnosis.

[e] Median.

relapse after complete resection during 3-y follow-up after primary surgery). Treatment of craniopharyngioma patients and their subsequent quality of life were affected by proximity and/or involvement of the tumor with the optic nerve or hypothalamic–pituitary axes, as well as treatment-related hypothalamic damage. In multivariate analysis of risk factors for the observed low event-free survival rates, the authors found that the risk for relapses after complete resection was 80% lower compared to incomplete resection. The risk for progression was 88% lower in irradiated patients when compared with patients without or before irradiation (175). Follow-up studies of quality of life in children after complete resection of craniopharyngioma revealed that quality of life also depends on the experience of the operating neurosurgeon (77, 103, 104).

X. Risk Factors and Treatment for Recurrence

Age at tumor diagnosis does not seem to affect the risk of recurrence (57, 91, 121, 176). However, this conclusion is

Table 5. Early Versus Delayed Radiation Therapy/Impact on Progression-Free and Overall Survival

First Author (Ref.)	No. of Patients (% of Children at Dgx)	Early RT	RT at Relapse
Sung (290)	10 (100)[b]	NR	70.9%, 10 y OS
Regine (271)	58 (33)[a]	78%, 20 y OS	25%, 20 y OS
Stripp (268)	40 (median age, 8.5 y; range, 1.5–24.8 y)	83%, 10 y OS	86%, 10 y OS
Tomita (211)	30 (100)[a]	71%, 5 y PFS	90%, 5 y PFS
Moon (180)	50 (30)[b]	91.3%, 10 y PFS	91.2%, 10 y PFS
Lin (213)	31 (100)	100%, 10 y LC	32%, 10 y LC

Abbreviations: RT, radiotherapy; OS, overall survival; PFS, progression-free survival; LC, local tumor control; Dgx, diagnosis; NR, not reported.

[a] Considered children <16 years old unless otherwise specified.

[b] Considered children <20 years old.

frequently based on analyses of heterogeneous single-center cohorts consisting of both childhood- and adult-onset craniopharyngioma patients (55, 78, 89, 119, 175, 177, 178). Still, the age at presentation may affect the risk of recurrence when comparisons are performed within childhood populations only (176, 179). In a series of 75 children, De Vile et al (177) found that an age less than 5 years was a significant predictive factor for recurrence. No gender differences have been detected (57, 91). Weiner et al (176) did not observe an effect of tumor size on the relapse rates.

The management of recurrent tumors remains difficult because scarring from previous operations or radiation decreases the possibility of successful excision. In such cases, the success rate of total removal drops dramatically (0–25%) when compared with primary surgery (57, 80, 178), and there is also increased perioperative morbidity (80, 180) and mortality (10.5–24%) (57, 80), suggesting that for many recurrent lesions, radio-oncological treatment options should be considered.

The beneficial effect of radiotherapy (preceded or not by second surgery) in recurrent lesions has been clearly shown. There was also no significant difference in tumor control among patients offered adjuvant radiotherapy after primary surgery and those receiving irradiation for recurrence (180, 181) (Tables 5 and 6). Recurrent lesions with significant cystic components not amenable to total extirpation may be treated by repetitive aspirations through a reservoir (79, 81). Alternatively, ventriculo-cisternal cystostomy can be considered.

XI. Long-Term Outcome—Sequelae

A. Morbidities

1. Pituitary deficiencies

Pituitary hormone deficiencies are common in craniopharyngioma. At the time of diagnosis, 40 to 87% of children (4, 69, 70, 182) present with at least one hormonal

Table 6. Advantages and Disadvantages of Modern Treatment Technologies in Radiotherapy of Craniopharyngioma

Technology	Advantages	Disadvantages
Conventional 2-D radiotherapy	Reliable clinical data and long follow-up indicating high efficacy.	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 planning. Sparing of normal tissue.	Rigid head fixation, low patient numbers, and no long-term follow-up yet.
Fractionated proton beam therapy	Optimal coverage of tumor site, with maximal sparing of surrounding tissue.	Low 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 (Cyber Knife)	Only a 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 on tumor control. No long-term follow-up. Only selected clinical settings.
Intracavitary colloid isotope instillation	High tumor control rates for cystic components.	Only cystic tumors. Underdosage in solid components. Leakage possible. Detrimental effects on visual function reported.
Interstitial irradiation (iodine seeds)	Excellent dose conformity. Optimal protection of normal tissue.	Only a few clinical data published.

Abbreviations: IMRT, intensity-modulated radiation therapy; 2-D, two dimensional; 3-D, three-dimensional.

Modified from Ref. 104 with permission of the author and Frontiers Endocrinol.

deficit, and 17 to 27% (4, 70, 183) have been reported to have diabetes insipidus neurohormonalis. The rate of postsurgical pituitary hormone deficiencies increases due to the tumor's proximity or even involvement with the hypothalamic–pituitary axes (69, 70, 72, 92, 177, 183–185). Transient postsurgical diabetes insipidus occurs in up to 80 to 100% of all cases (69, 186). The rate of permanent postsurgical diabetes insipidus ranges between 40 and 93% (69, 70, 92, 104, 177, 183, 186–188).

In adult-onset craniopharyngioma patients, anterior pituitary deficiencies and diabetes insipidus are most common, and most patients present with hypopituitarism (8, 57, 182, 189). Endocrine dysfunction may worsen upon treatment. Mortini et al (190) 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. Postsurgical onset of diabetes insipidus was observed in 70% of their patients. The risk for new endocrine deficits appears to be lower after the transsphenoidal surgical approach (182, 190). Recovery of pre-existing pituitary dysfunction after surgery is rare. Most of the adult-onset craniopharyngioma patients suffer from partial or complete hypopituitarism as well as diabetes insipidus, with approximately 80% requiring the substitution of more than two pituitary hormones (8, 191).

GH deficiency has been described at the time of diagnosis in 26 to 75% of childhood craniopharyngioma (4, 188), and impaired growth, one of the primary manifestations of craniopharyngioma, often occurs years before diagnosis (72). GH deficiency after tumor treatment for childhood craniopharyngioma is found in about 70 to 92% of patients (72, 104, 192, 193), and a positive response to GH treatment is seen in most cases (194). Normal growth in childhood craniopharyngioma patients with proven GH deficiency is reported in the literature (195). In fact, childhood craniopharyngioma patients with hypothalamic involvement were found to achieve normal adult height more often than those without hypothalamic involvement (72). Although this phenomenon of "growth without GH" was described in childhood craniopharyngioma almost five decades ago (196), 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 (197–199), with leptin reported to function as a bone growth factor acting directly at the level of bone growth centers, independently of GH (197). Mechanisms by which insulin stimulates growth include its known anabolic effects. At high serum levels, insulin may bind to the IGF-1 receptor and induce growth, mediated by its actions to decrease IGF-binding protein 1 levels, resulting in increased levels of free IGF-1 (197). In support of this theory, obese childhood craniopharyngioma patients were found to present with higher height SD scores at the time of diagnosis and at last follow-up with no difference in hormonal substitution, including GH (200). In contrast, another study found that childhood craniopharyngioma patients who were growing despite GH deficiency had the same mean anthropometrical measures, body composition, and metabolic indexes, including insulin levels, as those requiring GH substitution (195).

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 (4), with some postsurgical improvement of vision in 41 to 48% of patients (69, 187). Risk factors for postsurgical visual impairment include tumor location in the prechiasmatic area and severe presurgical visual deficits (69, 184). Improved ophthalmological outcome has been detected in surgical cases using the transsphenoidal approach (187), 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 (92, 183, 193). Most of these sequelae are transient, and the total prevalence of long-term neurological complications is reported to be 8% (69), but it increases to 36% for large-sized tumors (183) and 30% when including both visual and neurological complications (186). See further information on these topics in *Section XI.A.10* (*Quality of life, neurocognitive outcome, and psychosocial functioning*).

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 (183). The rate of hypothalamic dysfunction dramatically increases after radical surgical treatment—in some series up to 65 to 80% (183, 186). Although presurgical evaluation

Figure 3.

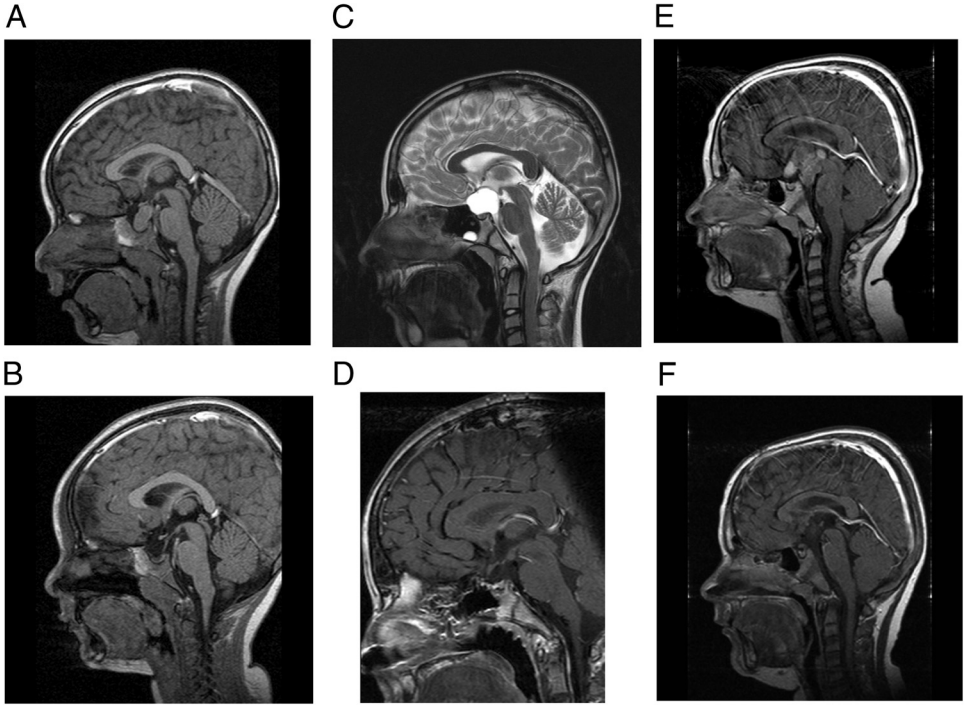

Figure 3. BMI and MRI at diagnosis and 36 months after surgery in 3 cases of childhood craniopharyngioma with different grade of hypothalamic involvement/lesion. A and B, Patient with craniopharyngioma confined to the intrasellar space (0° = no hypothalamic involvement, A; surgical lesion, B). BMI at diagnosis, −1.96 SD (15); BMI 36 months after complete resection, −1.62 SD. C and D, Patient with craniopharyngioma involving the anterior hypothalamus (I° = hypothalamic involvement, C; surgical lesion of the anterior hypothalamic area, D). BMI at diagnosis, +1.01 SD; BMI 36 months after complete resection, +0.59 SD. E and F, Patient with craniopharyngioma involving the anterior and posterior hypothalamus (II° = hypothalamic involvement, E; surgical lesion of the anterior and posterior hypothalamic area, F). BMI at diagnosis, +6.08 SD; BMI 36 months after complete resection, +6.79 SD. Arrows indicate mammillary bodies, defining the border between anterior and posterior involvement/lesion and craniopharyngioma. [Reproduced from H. L. Müller et al: Post-operative hypothalamic lesions and obesity in childhood craniopharyngioma: results of the multinational prospective trial KRANIOPHARYNGEOM 2000 after 3-year follow-up. *Eur J Endocrinol*. 2011;165: 17–24 (104), with permission. © European Society of Endocrinology.]

of hypothalamic damage is difficult, both clinically and radiologically (184), tumor involvement of the third ventricle and obstructive hydrocephalus are suggestive findings (69). A three-level clinical grading system for hypothalamic dysfunction has been suggested, based on the degree of obesity and hypothalamic tumor involvement (177).

Associated with high morbidity, suprachiasmatic lesions with hypothalamic involvement are difficult to treat. Surgical removal of tumor tissue beyond the mammillary bodies (ie, in the posterior hypothalamic area) endangers hypothalamic structures and may cause hypothalamic obesity (82, 104). 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 (104, 201–203). Fjalldal et al (204) 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 years (1–40 y) 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 craniopharyngioma (204). Taking these considerations into account, a novel classification of presurgical involvement and postsurgical lesions of hypothalamic structures based on MRI has been recently published (79). The classification is intended to help establish more risk-adapted surgical strategies (Figure 3) based on a grading of presurgical hypothalamic involvement and postsurgical hypothalamic lesions.

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 cranio-

pharyngioma patients often occurs years before diagnosis (72), with 12 to 19% of patients reported to be obese at diagnosis (4, 70, 186, 188). 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 (205). The degree of obesity frequently increases early after treatment, and rapid weight gain frequently occurs during the first 6 to 12 months after treatment (188, 200, 202). After treatment, the prevalence of severe obesity is higher, reaching up to 55% (70, 186–188, 195, 200, 206–208). Obesity and eating disorders result in increased risks of metabolic syndrome (195) and cardiovascular disease (203), including sudden death events (209), increased multisystem morbidity (189), and increased mortality (108, 186, 210–216).

Although the relation of severe obesity with hypothalamic lesions is obvious in craniopharyngioma patients (202, 203, 217), 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 (218). 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 (219). 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 body mass index (BMI) were found in childhood craniopharyngioma patients with a suprasellar tumor extension (220), 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 (221).

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 (221). 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 (205). 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 (222). 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, ie, frequent sleep-onset rapid eye movement phases (206, 223, 224). Medication with central stimulating agents (methylphenidate, modafinil) had a markedly beneficial effect on daytime sleepiness in these patients (223). 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 (225)

treated five patients with childhood craniopharyngioma and severe hypothalamic obesity (age range, 6.0–9.8 y) with the central stimulating agent dextroamphetamine for the purpose of weight reduction. Dextroamphetamine therapy stabilized the BMI of patients, and the patients' parents reported marked improvements in their children'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 compared to controls (202, 226, 227) that could not be explained by differences in terms of body composition. This energy intake/resting-energy expenditure ratio was lower in those with tumors involving the third ventricle (202). Impaired physical activity is also likely to contribute to an overall lowering of total energy expenditure (202, 203, 221, 226). Further factors potentially contributing to decreased physical activity are neurological and visual deficits, psychosocial difficulties, and increased daytime sleepiness.

6. Autonomous nervous system

Lustig et al (228, 229) 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 analog octreotide, which suppresses β-cell activity (228).

Several reports (230, 231) hypothesized that decreased physical activity and severe obesity in patients with childhood craniopharyngioma are likely related to impaired central sympathetic output. For instance, Roth (232) observed reduced urine concentrations of catecholamine metabolites correlating with the degree of obesity and the level of physical activity.

7. Appetite regulation

Roth et al (233, 234) 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. 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 ofperipheral α-melanocyte-stimulating hormone in childhood craniopharyngioma obesity has also been reported (235).

Functional MRI was used in childhood craniopharyngioma patients to examine the hypothesis that hypothalamic damage due to the tumor and its treatment results in enhanced perception of food reward and/or impaired central satiety processing (236). After the test meal, controls showed suppression of activation by food cues, whereas childhood craniopharyngioma patients showed trends toward higher activation. The authors concluded that perception of food cues appears to be altered in hypothalamic obesity, especially after eating, ie, in the satiated state. It was also concluded that functional MRI is encouraging for performing future mechanistic studies of the brain response to food cues and satiety in patients with hypothalamic obesity due to craniopharyngioma.

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 (237, 238). Use of dextroamphetamine intervention starting 10 months after surgery and lasting 24 months was shown to diminish continuous weight gain and to stabilize BMI (225); importantly, spontaneous physical activity increased significantly. Even shorter periods of dextroamphetamine treatment have caused asubjective improvement in daytime sleepiness (239). Also, Elfers and Roth (240) observed beneficial effects of central stimulating agents (particularly methylphenidate) on weight development in craniopharyngioma patients.

Sibutramine is a neurotransmitter reuptake inhibitor that reduces the reuptake of serotonin, norepinephrine, and dopamine, thereby increasing the levels of these substances in synaptic clefts that help enhance satiety. Sibutramine has been widely used to treat obesity, leading to a weight loss of 7 to 10% when combined with a regulated diet. Sibutramine was tested in a randomized, placebo-controlled, crossover trial in patient cohorts with different obesity syndromes (241). Although the drug was well tolerated and tested safe in these trials, the weight loss response in patients with hypothalamic obesity was less pronounced in comparison to other participants (such as trisomy 21 and Prader-Willi syndrome). Although the ef-

fect on BMI was promising, sibutramine has been taken off the market due to adverse side effects, and further clinical trials are not expected.

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 (242). Parasympathetic stimulation causes insulin secretion by way of direct activation of β-cells as well as promoting adipogenesis. Because insulin is an anabolic hormone, it has been suggested to be an important driver of weight gain in hypothalamic obesity. Octreotide is a somatostatin analog and thus causes reduction in insulin secretion. Lustig et al (228) used octreotide in a double-blind, randomized, controlled study in children with hypothalamic obesity and demonstrated moderate reductions in weight gain. 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 (243). 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.

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 (244–246). An instant improvement of binge-eating behavior in patients with childhood craniopharyngioma immediately after laparoscopic adjustable gastric banding was observed, but it failed in long-term weight reduction. Nevertheless, weight stabilization could be achieved during regular follow-up monitoring (247).

In a systematic review and meta-analysis of the literature, Bretault et al (248) analyzed the 12-month outcome after bariatric surgery for hypothalamic obesity due to craniopharyngioma treatment. At 1 year, six of 18 cases with follow-up data had lost more than 20% of their initial weight; they had undergone 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 laparoscopic adjustable gastric banding, except one Roux Y gastric bypass case. These findings indicate that Roux Y gastric bypass, sleeve gastrectomy, and biliopancreatic diversion are the mostefficient bariatric procedures for weight reduction in hypothalamic obesity of childhood craniopharyngioma patients. However, treatment with invasive, nonreversible bariatric methods is controversial in the pediatric population because of medical, ethical, and legal considerations (247, 249, 250).

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 (251).

10. Quality of life, neurocognitive outcome, and psychosocial functioning

Quality of life 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 (70, 178, 186, 252–254). 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 (186). Other reported challenges included somatic complaints such as reduced mobility, pain, and self-care (92, 186). 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 (193, 255).

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 third ventricle involvement at presentation—are reported in the literature to complicate both pre- and postsurgical conditions and, therefore, survival and quality of life outcomes in these patients (77, 82, 177, 179). Treatment strategies have also been implicated (see *Section IX.D*), 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 quality of life outcome (70, 92, 178, 183, 184, 186, 252). Hypothalamic dysfunction has been found to have the most important negative impact on social functioning, physical ability, and body image (186, 200, 252).

Long-term neurocognitive complications after treatment for craniopharyngioma include cognitive problems, particularly those affecting executive function, attention,

episodic memory, and working memory (186, 193, 255–260). In a recent report, Oezyurt et al (261) 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 (193). Neurocognitive deficits include memory disturbances, slower cognitive speed, attention problems, and behavioral instability (193, 255, 256, 258, 259, 262). Although intact intellectual functioning has been reported in up to 82% of patients, visual memory is impaired despite normal visual-spatial abilities (193, 255). The acquired deficits in higher cognitive processing such as attention problems are considered precursors to poor academic achievement.

Despite over a quarter of a 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 (263, 264). In a case report of a 2-month intervention using a combination of goal management therapy and naturally occurring distractions within the patients' work environment, significant improvements in cognitive tests requiring organized behavior were reported. Social, emotional, and/or behavioral problems, most notably aggression, have been reported (186, 257, 265). Despite their occurrence, the assumption of the biological underpinning of behavioral disturbances in these patients appears to result in limited attempts to effectively manage these disturbances with intervention. Behavioral treatment was used for severe aggressive behaviors (264); the intervention included functional behavioral analysis followed by differential reinforcement of alternative behaviors and extinction of dysfunctional conditioned responses, with the goal of decreasing the frequency of aggressive behavior. Aggressive behavior subsequently decreased to below 88% of baseline levels, and adaptive behaviors were found to increase significantly. These results suggest that the patients' aggression was maintained by inadvertent social reinforcement. 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 (266).

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 (90, 267). 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 (267). 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 Kramer (181) reported a 13.7% rate of cerebrovascular events, all in irradiated cases receiving over 61 Gy. No cerebrovascular clinical events have been reported in any other series of conventionally fractionated radiotherapy for craniopharyngioma, including those with large patient numbers (57, 91, 110, 121, 122, 180, 268). Fusiform dilatation of the carotid artery on postoperative MRI has been noted in 10 to 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 (269, 270).

Nontraditional cardiac risk factors have also been described in patients with craniopharyngioma. A small retrospective study of 12 craniopharyngioma patients found that half of them had at least one abnormality of cardiac structure, function, or rhythm, specifically prolonged QT interval in 25% of the cohort (209). Besides cardio- and cerebrovascular mortality, other main underlying causes of death in patients with craniopharyngioma are respiratory complications (7) and infections (189).

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 years (91). Three long-term survivors (2%) died of systemic malignancies with unspecified diagnoses. Overall, only four cases of second malignancies have been reported (90, 117, 127, 271), comprising two in-field glioblastomas (117, 271), one in-field glioma with unspecified grade of malignancy (90), and one posterior fossa meningioma (127).

B. 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 (189, 272) (Table 7). When assessing mortality in patients with craniopharyngioma, the literature indicates that it is

Table 7. Studies Reporting Overall Survival Rates in Craniopharyngioma Patients

First Author (Ref.)	No. of Patients (% Children at Diagnosis)[a]	Follow-Up Period	OS Rates, %[b]		
			5 y	10 y	20 y
Bunin (21)	285 (29)[c]	1985–1988 and 1990–1992	80	NA	NA
Stripp (268)	76[d]	1974–2001	96	85	NA
Bülow (272)	60 (43)[c]	1951–1988	NA	68	NA
Pereira (189)	54 (25)	1965–2002 (median, 10 y)	95	85	85
Müller (4)	385 (100)[e]	1980–2001	91	87	NA
Regine (271)	58 (33)[a]	1958–1982	54/84[f]	51/72[f]	62
Tomita (211)	54 (100)[a]	1984–2003	93	90	NA
Sung (290)	109 (40)[g]	1950–1977	67[h]	53[h]	NA
Fisher (212)	30 (100)[e]	1980–1996	95	NA	NA
Habrand (117)	37 (100)[g]	1969–1992	91	65	NA
Lin (213)	31 (100)[i]	1970–2002 (median, 6.5 y)	NA	96	NA
Kalapurakal (214)	25 (100)[g]	1983–1996 (median, 10 y)	NA	100	NA
Poretti (186)	25 (100)[a]	1980–2002 (median, 11 y)	NA	92	NA
Scott (215)	61 (100)[j]	1970–1990	NA	91	NA
Hetelekidis (90)	61 (100)[j]	1970–1990 (median, 10 y)	NA	91	NA
Khafaga (216)	56 (100)[e]	1975–1996	NA	65	NA
De Vile (177)	75 (100)	1973–1994 (median, 5 y)	NA	88	NA
Karavitaki (57)	121 (35)[a]	1964–2003 (median, 8.6 y)	91	90	NA
Van Effenterre (178)	122 (24)[a]	1975–2000	92	85	NA
Fahlbusch (80)	148 (20)[a]	1983–1997	NA	93	NA
Rajan (91)	173 (26)[a]	1950–1986 (median, 12 y)	NA	77	66
Bartlett (274)	85 (35)[a]	1938–1970	NA	43	NA
Pemberton (121)	87 (32)	1976–2002	NA	86	70
Spoudeas (293)	NA	1991–2002	93	89	NA
Cohen (273)	33 (55)[a]	2001–2011	NA	97	NA

Abbreviations: NA, not applicable/available; OS, overall survival.

[a] Considered children <16 years old unless otherwise specified.

[b] Survival rates from diagnosis or initial operation/radiotherapy treatment particular to study.

[c] Considered children ≤20 years old.

[d] Percentage of children not reported; patients' age at diagnosis ranged from 1.5–24.8 years, with a median of 8.5 years.

[e] Considered children ≤18 years old.

[f] Survival rates of 54 and 51% in adults and 84 and 72% in children at 5 and 10 years, respectively.

[g] Considered children ≤15 years old.

[h] Survival rates of 55 and 40% in adults and 83 and 72% in children at 5 and 10 years, respectively.

[i] Patients' age at diagnosis ranged from 1.1–20 years with a median of 8.1 years.

[j] Considered children ≤21 years old.

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 to 96% at 5 years (4, 84, 117, 200, 211, 212, 271) and 65 to 100% at 10 years (4, 70, 90, 117, 177, 186, 210, 211, 213–216, 271, 273) and average 62% at 20 years (181). In adults or a mixed-age-range population (adults and children) series, the overall survival rates range from 54 to 96% at 5 years (29, 57, 80, 91, 121, 178, 189, 268, 271, 274), from 40 to 93% at 10 years (57, 80, 91, 121, 178, 183, 189, 268, 271, 272, 274), and from 66 to 85% at 20 years (91, 121, 189) (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 (29, 80, 271, 272); others have found a better outcome in older patients (91, 179), whereas still other studies report no difference between pediatric and adult populations (55, 57, 121, 268, 275). The role of gender as a prognostic factor is not established; some authors report a higher mortality among females (189, 272), but others have not found any gender differences (57, 211, 268, 275). One of the two studies reporting higher mortality rates in females suggested a possible role of estrogen deficiency (189), but the other study did not consider that unsupplemented gonadal insufficiency had a significant impact on enhanced mortality (272).

Disease-related mortality can even occur many years after treatment. Causes of late mortality include those directly related to the tumor or its treatment such as progressive disease with multiple recurrences, chronic hypo-

thalamic insufficiency, hormonal deficiencies, cerebrovascular disease, and seizures (177, 183, 184, 186, 210). Other causes have been described, including decreased bone mineral density and nonalcoholic steatohepatitis, leading to liver cirrhosis in some cases (69, 186, 207, 210, 276–279). 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 quality of life 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, patients with childhood craniopharyngioma have a 3- to 19-fold higher cardiovascular mortality in comparison to the general population, and female childhood craniopharyngioma patients have an even higher risk (8).

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 (55). The histological type as a prognostic factor is also controversial; better 5-year survival rates have been found in the squamous epithelial type vs the adamantinomatous and combined histological types (280). Higher perioperative deaths have also been reported in adult adamantinomatous tumors (281), but other authors have not found significant differences between the two histological types (176, 282). Several studies have described a more favorable prognosis whentumors lack calcification, especially in adult craniopharyngioma patients (55, 281), although no specific pathological feature predicted survival in childhood craniopharyngioma patients (212). In other studies, neither tumor histology (55, 57) nor tumor location (57, 211) had prognostic importance. In childhood craniopharyngioma patients, the use of modern imaging and 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 postsurgical survival at 10 years (117). It is not clear whether the presence of hydrocephalus constitutes a prognostic factor because increased mortality (179) and lack of association with mortality have been reported (57, 211, 212, 268).

XII. Adult-Onset Versus Childhood-Onset Craniopharyngioma

According to a recent study, there are no significant differences in neuroradiological characteristics of craniopharyngiomas between the childhood- and adult-onset types with the exception of lower rates of tumor calcification in adult-onset craniopharyngioma patients (190). In some studies, hydrocephalus occurred less frequently in adults than in children; however, other authors reported no differences in this regard (57, 178). According to the literature, age-dependent differences between childhood-onset and adult-onset craniopharyngioma are reported to be related to histological diagnosis, biological behavior, clinical manifestations, treatment options, and follow-up period (191, 283, 284).

Growth retardation and short stature are also reported as predominant manifestations of childhood craniopharyngioma (72). Due to high overall survival rates and irradiation in childhood craniopharyngioma, the above-cited literature strongly advises considering the risk of development of second malignancies in long-term follow-up.

The Kendall-Taylor et al (191) study compared childhood-onset craniopharyngioma patients with adult-onset craniopharyngioma patients and reported a poor state of health and quality of life in both cohorts. Most childhood- and adult-onset craniopharyngioma patients displayed pituitary insufficiency, with 60% suffering from diabetes insipidus. Nearly all patients were overweight or obese, reporting a consequential poor quality of life (191).

XIII. Questions and Treatment Perspectives

A. Surgical treatment strategies—degree of resection

One of the biggest challenges in treating craniopharyngioma is identifying the best candidates for a radical vs conservative treatment approach (9). Experiential expertise in large centers has increased the likelihood of safe gross total resection, evidenced by two reports representing historically different attitudes: the first at Necker Hospital (Paris, France) (88), which is more surgically oriented; and the second in North America (110), which is more oriented toward a conservative approach. The North American experience shows that most recent cases now receive moderate to aggressive surgery, and only 42% have limited surgery before irradiation. The Necker authors (285) show in a contemporary series that 96% of their recent cases achieve complete (23%) or subtotal resection (73%) and that radiotherapy is performed in 50% of cases after subtotal resection. It appears that there is a trend toward radiotherapy in centers with past predominantly surgical approaches and toward more radical surgical treatment strategies in centers historically surgically conservative-oriented (286). There are current prospective studies under way on a national and multinational level to adopt strategies tailored to risk factors for morbidity and quality of life (285, 287, 288).

Elowe-Gruau et al (87) recently reported on a single-institute treatment comparison of patients with child-

hood-onset craniopharyngioma. A historical cohort of 60 children underwent extensive resection surgery between 1985 and 2002, and a prospective cohort of 65 patients underwent a hypothalamus-sparing surgical strategy between 2002 and 2010. During this second time period, the indication for hypothalamus-sparing surgery was made using an algorithm that graded presurgical hypothalamic tumor involvement (285). At last follow-up, patients treated by hypothalamus-sparing surgery had a significantly lower prevalence of severe obesity (BMI $>$ 3 SD) than patients treated by extensive resection surgery (28 vs 54%, respectively). The mean number of surgical procedures was the same for both surgical groups. In the multivariate analysis, preoperative hypothalamic involvement and hypothalamic-sparing surgery independently predicted the presence of severe obesity at last follow-up.

B. Controversy over time point of irradiation

In clinical practice, the literature indicates that the timing of postoperative residual tumor irradiation is both unclear and inconsistently regarded (84, 180, 181, 211, 268, 287, 289, 290). Some favor immediate postoperative irradiation in the event of life-impairing clinical conditions, proactively preventing tumor progression (92). On the other hand, some authors favor a wait-and-see procedure, delaying irradiation to reduce both its necessity and the negative consequences associated with radiation therapy. Some literature presents a strong, empirical argument that immediate postoperative irradiation significantly delays tumor progression (268). However, other literature reports that progression-contingent irradiation has proved to be effective because overall survival is statistically unaffected by this wait-and-see strategy (181). Three recent series retrospectively compared the immediate postoperative irradiation strategy with progression-contingent deployment (180, 211, 268). No differences in overall and progression-free survival were detected between immediate irradiation and progression-contingent treatment in the series evaluated by Moon et al (180). Relapse-free overall survival rates were 83 and 70% after 5 and 10 years, respectively, in the series analyzed by Tomita and Bowman (211). The corresponding numbers for patients after incomplete resection followed by immediate irradiation were 71 and 36% after 5 and 10 years, respectively. After incomplete resection without radiation therapy, the relapse-free survival rate after 5 years was merely 9%. Progression-contingent irradiation achieved similar final overall survival and progression-free survival rates of 90 and 70%, respectively, meaning progression-contingent irradiation in this series was highly effective (Table 5). However, it is also emphasized in the literature that the interpretation of these studies is difficult due to confounding factors in terms of indication for treatment and unknown factors regarding medical staff experience and state of facilities. Regardless of concerns over quality and completeness of data, the relevant endpoints in analysis of craniopharyngioma treatment should be the patients' quality of life and morbidity (2, 6, 82).

KRANIOPHARYNGEOM 2007, a prospective, childhood craniopharyngioma multinational trial (2–4, 83, 84, 288, 291), is currently evaluating craniopharyngioma patients' prognoses (quality of life, event-free survival, overall survival) following defined therapeutic strategies. A stratified randomization of two treatment arms is being conducted with respect to timing of postoperative irradiation (immediate radiotherapy vs radiotherapy at the time of progression) for the subgroup of patients $\geq$ 5 years of age at the time of incomplete resection. The schedule of prospective data collection and the set and definition of parameters in KRANIOPHARYNGEOM 2007 are based on a multinational European consensus (288).

C. Expertise

There are only a few studies that have analyzed the outcome of patients with craniopharyngioma in relation to the neurosurgeons' experience. Sanford (103) and Boop (292) reported a marked difference in outcome according to the neurosurgeons' experience with the condition.

The degree of obesity and quality of life based on reference assessment of tumor location and postsurgical hypothalamic lesions were analyzed in a recent report (104). Treatment was also analyzed regarding neurosurgical strategy and the neurosurgical center sizes based on patient load. Surgical lesions of anterior and posterior hypothalamic areas were associated with postsurgical obesity, negatively impacting quality of life in patients with surgical posterior hypothalamic lesions. Treatment in large centers was less radical, and the rates of complete resection and hypothalamic surgical lesions were lower than those of middle-sized and small centers (77). However, a multivariable analysis showed that preoperative hypothalamic involvement was the only independent risk factor for severe obesity (104).

Based on the most current literature presenting factors affecting the treatment and quality of life effects of craniopharyngioma, it is advisable to have a multidisciplinary team able to discuss diagnostic and treatment strategies, adopting the most sophisticated approaches feasible based on sufficient in-house surgical, radio-oncological, and psychosocial experience for treating patients with craniopharyngioma (6, 82).

XIV. Novel Risk-Adapted Strategies/ Treatment Algorithms

Novel risk-adapted treatment strategies (Table 8) are reportedly focusing on the following main goals: 1) relief of

Table 8. Novel Grading Systems and Treatment Algorithms for Craniopharyngioma Patients Based on MRI

First Author (Ref.)	n	FU, y	Grade 0 (0 degree)	Grade 1 (I^o)	Grade 2 (II^o)	Treatment Recommendation	Outcome Parameters
Puget (285)	65	3	No HI	HI (distortion/elevation) with negligible hypothalamic damage, the hypothalamus is still visible	Tumor spread to the hypothalamus, which was no longer identifiable.	0^o, GTR. I^o, attempt at GTR; if not achieved: 2nd surgery ± XRT. II^o, subtotal resection with hypothalamic preservation + XRT	Lower BMI and similar relapse rate in a prospective cohort treated according to algorithm compared with historical cohort
Garrè (44)	n.a.	n.a.	No HI	According to Puget *et al.* (285)	According to Puget *et al.* (285)	0^o + I^o, attempt at GTR by experienced surgeon; if not achieved, XRT. II^o, cyst drainage ± XRT (proton beam therapy at age <5 y)	n.a.
Müller (77, 104)	120	3	No HI	HI/lesion of the anterior hypothalamus not involving the MB and the hypothalamic area beyond MB.	HI/lesion of the anterior + posterior hypothalamic area, ie, involving the MB and the area beyond MB.	0^o, GTR. I^o, attempt at GTR; if not achieved, XRT. II^o, subtotal resection with hypothalamic preservation + XRT.	Higher BMI and lower quality of life in the II^o cohort treated by GTR resulting in posterior hypothalamic lesions.
Flitsch (79)	n.a.	n.a.	No HI	According to Müller *et al.* (77, 104), specifying sections below and above the diaphragm sellae.	According to Müller *et al.* (77, 104).	0^o, GTR. I^o, attempt at GTR -- transsphenoidal approach; if not achieved, XRT. II^o, subtotal resection with hypothalamic preservation -- transcranial approach, followed by XRT.	n.a.
Fjalldall (204)	42	20	No HI	Suprasellar growth, not toward or into the 3rd ventricle (non-TGTV).	Suprasellar growth toward or into the 3rd ventricle (TGTV).	Non-TGTV, GTR. TGTV, subtotal resection with hypothalamic preservation + XRT.	Lower cognitive performance in TGTV patients treated by GTR.
Spoudeas (293)	n.a.	n.a.	No HI	Tumor size (≤2–4 cm), no hydrocephalus, no hypothalamic syndrome, no breech 3rd ventricle	Retrochiasmatic tumor, (>4 cm), hydrocephalus, hypothalamic syndrome ± breech 3rd ventricle	0^o, GTR; I^o, consider GTR. II^o, limited resection + XRT.	n.a.

n, size of cohort; FU, follow-up; HI, hypothalamic involvement; n.a., not analyzed; GTR, gross-total resection; XRT, irradiation; TGTV, growth toward 3rd ventricle; MB, mammillary bodies.

raised intracranial pressure; 2) reversal of visual compression symptoms; 3) restoration or substitution of pituitary hormone deficits plus all other supplement-supportive measures; and 4) prevention of tumor regrowth/progression, while minimizing acute and long-term morbidity and mortality. With regard to the last goal, strategies aiming at gross total resection in craniopharyngioma patients with hypothalamic tumor involvement are not recommended by the current literature. Accordingly, several recommended treatment algorithms reflecting this hypothalamus-sparing aspect (Table 8) have been published recently (44, 77, 79, 87, 104, 286, 293, 294).

Puget et al (285) published an algorithm for neurosurgical treatment of childhood craniopharyngioma patients (Figure 4), which recommends a hypothalamus-sparing surgical strategy based on the grading of hypothalamic tumor involvement in preoperative MRI. The authors recently reported (87) that patients treated according to this algorithm using a hypothalamus-sparing surgical approach had similar relapse rates and a lower prevalence of severe obesity than patients treated by gross-total resection (28 vs 54%, respectively). This is the first report in the literature (87) proving the efficacy and tolerability of a hypothalamus-sparing strategy by comparing cohorts treated at a single institution by the same experienced surgical team (6), and thus eliminating the bias of surgical experience on outcome analysis.

Garrè et al (44) used this grading system of hypothalamic involvement (285) and published a modified algorithm for risk-adapted treatment strategies in childhood craniopharyngioma. The authors emphasized the treatment by experienced neurosurgical teams and suggested proton beam therapy, especially for young patients (<5 y of age) after limited hypothalamus-sparing surgery.

Müller et al (104) suggested a treatment strategy based on pre- and postsurgical grading of hypothalamic tumor involvement/damage in MRI (Figure 4). The assessment of the tumor extension toward the mammillary bodies is considered essential for the grading into anterior or posterior hypothalamic involvement/lesion. According to their report, patients with postsurgical lesions of the posterior hypothalamus presented with a higher BMI and lower self-assessed quality of life during prospective follow-up. Flitsch et al (79) modified this grading system (104) and

Figure 4.

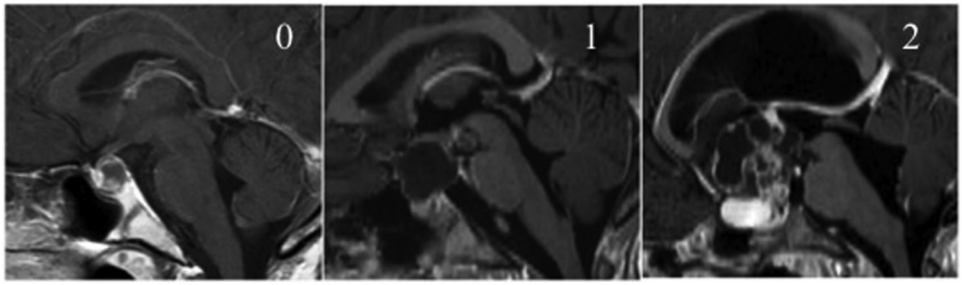

Figure 4. Three-grade classification system of preoperative MRI. Grade 0, tumor not in contact with the hypothalamus; grade 1, tumor in contact with the hypothalamus, with negligible hypothalamic damage; grade 2, tumor spread to the hypothalamus, which is no longer identifiable. [Reproduced from S. Puget: Treatment strategies in childhood craniopharyngioma. *Front Endocrinol (Lausanne)*. 2012;3:64 (286), with permission. © Frontiers Media S.A.].

published an algorithm suggesting different surgical approaches (transsphenoidal vs transcranial) based on preoperative MRI (Figure 5).

Figure 5.

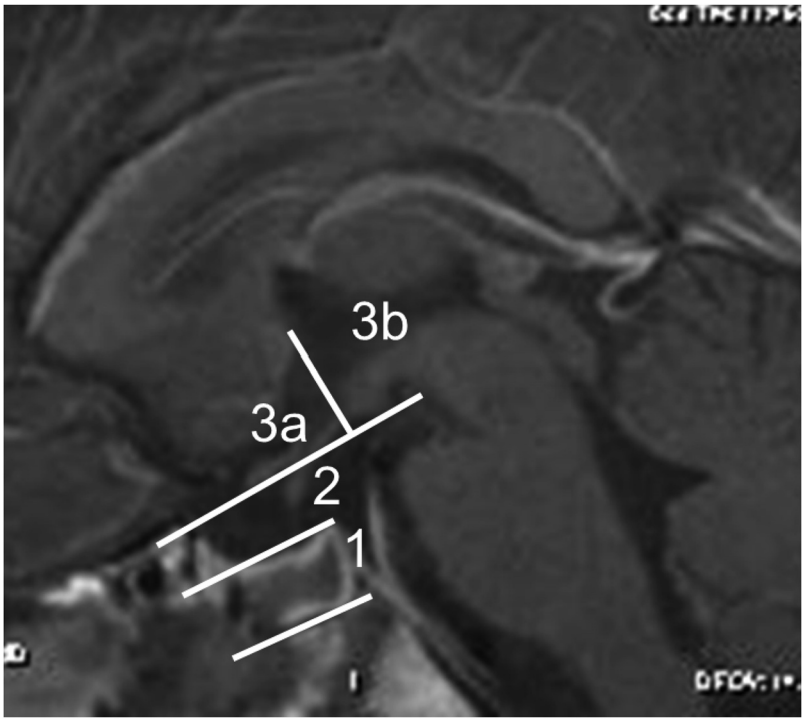

Figure 5. Sagittal MRI of the midline. Note suggestion of a classification system of craniopharyngiomas by preoperative MRI criteria. The intra- and suprasellar region can be divided into three sections. Section 1 is limited by the diaphragma sellae, Section 2 is below the optic chiasm and the mammillary bodies, and Section 3 is above the chiasm and mammillary bodies, subdivided into an area anterior and posterior of the mammillary bodies. In this particular patient, a transsphenoidal surgery of a type 1 craniopharyngioma had been performed previously. Section 1 is usually reached by the transsphenoidal route, whereas Sections 3a and 3b are mostly reserved for transcranial procedures. Depending on the tumor extension, Section 2 can be reached by transcranial as well as transsphenoidal procedures. [Modified from J. Flitsch et al: Surgical strategies in childhood craniopharyngioma. *Front Endocrinol (Lausanne)*. 2011;2:96 (79), with permission. © Frontiers Media S.A.].

Fjalldal et al (204) published a grading system on hypothalamic involvement in childhood craniopharyngioma and could demonstrate that gross total resection in craniopharyngioma with extension into the third ventricle results in lower cognitive performance and psychosocial health.

Spoudeas et al (293) suggested a hypothalamus-sparing surgical strategy based on a grading system that includes tumor size, hypothalamic involvement, and the presence of hydrocephalus. Based on this grading system, Mallucci et al (294) published a treatment algorithm, suggesting a two-staged surgical approach with initial relief of cystic pressure and thereby down-staging the risk grade in appropriate cases.

All of the above-mentioned treatment strategies recommend that: 1) for cases of hypothalamic tumor involvement, limited surgical approaches and postoperativeradiotherapy are advisable; and 2) treatment of craniopharyngioma should be confined to experienced multidisciplinary teams.

XV. Conclusions

Risk-adapted surgical strategies at initial diagnosis of craniopharyngioma should aim at a maximal degree of resection keenly focused on respecting the integrity of optical and hypothalamic structures to prevent

severe sequelae and therein minimizing consequences that could negatively impact patient quality of life. In cases of hypothalamic involvement, hypothalamus-sparing surgical strategies are recommended to prevent hypothalamic damage and associated severe sequelae. It is broadly reported that local irradiation of residual tumor is efficient in preventing tumor progression.

Because initial hypothalamic tumor involvement, especially of posterior hypothalamic structures, is reported to have an a priori effect on the clinical course (72, 104), craniopharyngioma should be recognized as a frequently chronic disease requiring constant monitoring of the consequences and medical resources for treatment in order not only to provide optimal quality of life for patients, but also to garner additional information with the intent of minimizing what at present are severe consequences of both the disease and its treatment (6, 82).

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