Very long-term sequelae of craniopharyngioma

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Abstract

Objective: Studies investigating long-term health conditions in patients with craniopharyngioma are limited by short follow-up durations and generally do not compare long-term health effects according to initial craniopharyngioma treatment approach. In addition, studies comparing long-term health conditions between patients with childhood- and adult-onset craniopharyngioma report conflicting results. The objective of this study was to analyse a full spectrum of long-term health effects in patients with craniopharyngioma according to initial treatment approach and age group at craniopharyngioma presentation.

Design: Cross-sectional study based on retrospective data.

Methods: We studied a single-centre cohort of 128 patients with craniopharyngioma treated from 1980 onwards (63 patients with childhood-onset disease). Median follow-up since craniopharyngioma presentation was 13 years (interquartile range: 5–23 years). Initial craniopharyngioma treatment approaches included gross total resection ($n=25$), subtotal resection without radiotherapy ($n=44$), subtotal resection with radiotherapy ($n=25$), cyst aspiration without radiotherapy ($n=8$), and ⁹⁰Yttrium brachytherapy ($n=21$).

Results: Pituitary hormone deficiencies (98%), visual disturbances (75%) and obesity (56%) were the most common long-term health conditions observed. Different initial craniopharyngioma treatment approaches resulted in similar long-term health effects. Patients with childhood-onset craniopharyngioma experienced significantly more growth hormone deficiency, diabetes insipidus, panhypopituitarism, morbid obesity, epilepsy and psychiatric conditions compared with patients with adult-onset disease. Recurrence-/progression-free survival was significantly lower after initial craniopharyngioma treatment with cyst aspiration compared with other therapeutic approaches. Survival was similar between patients with childhood- and adult-onset craniopharyngioma.

Conclusions: Long-term health conditions were comparable after different initial craniopharyngioma treatment approaches and were generally more frequent in patients with childhood- compared with adult-onset disease.

*European Journal of
Endocrinology*
(2017) **176**, 755–767

Introduction

Craniopharyngiomas are benign (supra)sellar tumours of epithelial histology that often exhibit calcifications and fluid-filled cysts (1). They affect both children and adults, and have peak incidences between 5–9 and 40–44 years of age (2). Since their discovery in 1857 by Von Zenker (3), there has been a controversy about their aetiology, pathogenesis and optimal therapeutic approach (4). In general, craniopharyngioma treatment aims to provide long-term survival and disease control while preserving quality of life by minimizing tumour- and treatment-related morbidity. This is challenging due to close proximity of the tumour to vital brain structures, like the hypothalamic–pituitary system and visual pathways (1). Craniopharyngiomas are generally treated with neurosurgical excision with or without postoperative radiotherapy. Alternative treatment options include intracystic appliance of beta-emitting isotopes or chemotherapeutic substances, as well as stereotactic radiosurgery (5). Although craniopharyngioma treatment is predominantly individualized based on tumour and patient characteristics, the aggressiveness of the therapeutic approach varies from centre to centre (6). Some centres favour initial extensive excision whereby preserving hypothalamic and optic functions (7, 8, 9, 10, 11, 12, 13, 14, 15), while other centres prefer a more conservative approach comprising limited resection or cyst decompression (16, 17, 18, 19, 20).

Although recent studies on craniopharyngioma report encouraging 10-year overall survival rates between 40 and 95% (10, 21, 22, 23, 24, 25), serious long-term health conditions related to tumour and treatment are frequent (10, 20, 22, 23, 24, 26, 27, 28, 29, 30, 31), and significantly impair quality of life (28, 32). Most studies assessing long-term health effects in patients with craniopharyngioma are limited by short follow-up durations of less than ten years (10, 20, 22, 23, 24, 25, 26, 27, 32, 33, 34). Furthermore, only a few studies compare long-term health conditions according to initial craniopharyngioma treatment approach (17, 35, 36, 37). Moreover, studies comparing long-term health effects between patients with childhood- and adult-onset craniopharyngioma report conflicting results (28, 30, 36).

The objective of the present study is to analyse a full spectrum of long-term health conditions in patients with craniopharyngioma according to initial treatment approach and age group at craniopharyngioma presentation.

Subjects and methods

Participants

Patients who were diagnosed with and/or treated for craniopharyngioma at the Erasmus University Medical Centre were eligible for participation in this cross-sectional study based on retrospective data. In order to reduce heterogeneity in our study population attributable to time-related differences in craniopharyngioma treatment, neuroimaging and supportive care, we chose to include only patients with craniopharyngioma treated from 1980 onwards. Our local institutional review board approved this study and all patients gave their informed consent.

Data collection

Patients were identified by a computer-based search in the electronic patient files. This search yielded 145 patients with craniopharyngioma of whom 128 were treated from 1980 onwards. Of these 128 patients, 63 were <18 years of age (i.e. childhood-onset), and 65 were ≥18 years of age (i.e. adult-onset). Patients presenting with craniopharyngioma between 1978 and 2015 were followed-up for a median of 13 years (interquartile range: 5–23 years). Diagnoses of all but three craniopharyngiomas were histologically verified. Data regarding baseline characteristics, presenting symptoms, hydrocephalus, tumour localization and consistency, treatment, long-term health conditions and survival were extracted from the medical records.

Craniopharyngioma localization and characteristics

Data regarding craniopharyngioma localization and consistency at diagnosis were obtained from neuroimaging and neurosurgery reports. Craniopharyngioma localization was defined as intrasellar, suprasellar or both intra- and suprasellar. Craniopharyngioma consistency was characterized as unicystic, multicystic or solid. Computed tomography and magnetic resonance imaging became available in our institution in 1976 and 1990 respectively.

Craniopharyngioma treatment

Initial craniopharyngioma treatment approaches were subdivided in gross total resection ($n=25$), subtotal

resection without radiotherapy ($n=44$), subtotal resection with radiotherapy ($n=25$), cyst aspiration without radiotherapy ($n=8$) and ^{90}Y trium brachytherapy ($n=21$). Three patients were treated with neurosurgical excision but had an unknown degree of resection and two patients were treated with other therapeutic approaches (radiotherapy only ($n=1$), cyst aspiration with radiotherapy ($n=1$)). These latter five patients were excluded from the analyses according to initial craniopharyngioma treatment approach. Gross total resection was defined as the complete removal of the craniopharyngioma as documented by the neurosurgeon, without residual disease on postoperative imaging. In each patient, the initial therapeutic approach was based on the treating physicians' preferences. Since the nineties, all patients were systematically discussed in multidisciplinary meetings by specialists in (paediatric) neurosurgery, (paediatric) endocrinology, paediatric neurology, paediatric oncology, radiation-oncology and neuroradiology.

Long-term health conditions

Visual disturbances, epilepsy requiring treatment, neurological deficits, cognitive impairment, behavioural changes, psychiatric conditions requiring treatment (postoperative delirium excluded), weight status, obstructive sleep apnoea, pituitary hormone deficiencies, secondary neoplasms and cardio- and cerebrovascular events were studied as outcomes reflecting long-term health conditions. Visual disturbances were diagnosed based on ophthalmic examinations. Visual acuity was determined after correction for refraction disorders. Visual field defects were diagnosed with Goldmann perimetry. Neurological deficits were classified into two categories (i.e. mild and severe) based on their reported impact on independent daily living. Deficits that had no impact were classified as mild and deficits that compromised independent daily living were classified as severe. Cognitive impairment and behavioural changes were considered to be present if documented in the patient files. Weight status was classified according to body mass index. Obstructive sleep apnoea was diagnosed by polysomnography in patients with suspected sleep disordered breathing. Pituitary hormone deficiencies were confirmed by formal pituitary function testing in all patients. In ten patients, the pituitary gland was completely removed during neurosurgical excision of the craniopharyngioma.

Survival

Overall and recurrence-/progression-free survival were calculated since initial craniopharyngioma treatment. Craniopharyngioma recurrence/progression was diagnosed with neuroimaging. Recurrence was defined as reappearance of the craniopharyngioma after gross total resection. Progression was defined as re-growth of the craniopharyngioma after subtotal resection, irradiation, cyst aspiration or ^{90}Y trium brachytherapy. Follow-up neuroimaging was performed regularly, based on physician's preference and clinical judgement. The cause of death was classified as directly related to the craniopharyngioma itself or not.

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS 24). Continuous variables were described as median and interquartile range; discrete variables as frequencies and percentages. Evaluations were based on the number of patients with available data. Comparisons according to initial craniopharyngioma treatment approach were performed by one-way analyses of variance for continuous variables and Chi-squared tests for discrete variables. In case the assumptions were not met, Kruskal–Wallis tests and likelihood ratio statistics were used. Comparisons between patients with childhood- and adult-onset craniopharyngioma were made by Student's *t*-test for continuous variables and Chi-squared tests for discrete variables. Mann–Whitney *U* tests and likelihood ratio statistics or Fisher's exact tests were used in case the assumptions were not met. Overall and recurrence-/progression-free survival were estimated by Kaplan–Meier methods. Log-rank tests were used to compare survival curves. In case statistical significance was reached in a variable concerning more than two groups, Bonferroni-corrected *post hoc* analyses were performed to specify subgroup-related differences. Because certain long-term health conditions may only become apparent after a prolonged follow-up period, and because craniopharyngioma management may have evolved over time due to advances in treatment, neuroimaging and supportive care, we investigated the influence of the treatment decade (i.e. 1980–1989, 1990–1999, 2000–2009, or ≥ 2010) and follow-up duration since initial craniopharyngioma treatment on the development of long-term health effects using multivariable logistic regression models including treatment decade and follow-up duration as independent variables. We investigated the influence of treatment decade on survival by log-rank

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tests for trend. A P -value <0.05 (two-tailed) was considered statistically significant.

Results

Presenting symptoms

Presenting symptoms in patients with craniopharyngioma are shown in Table 1. Visual disturbances, pituitary hormone deficiencies and headaches were the most common disease manifestations and occurred in 87, 71, and 68% of the patients respectively. Hypogonadotropic hypogonadism was the most common pituitary hormone deficiency and it affected 60% of the patients. Diabetes insipidus was found in 7% of the patients. Underweight and obesity affected 10% and 12% of the patients respectively. Two patients (both with childhood-onset craniopharyngioma) presented with blindness. Patients with childhood-onset craniopharyngioma presented significantly more growth hormone deficiency (53% vs 27%, $P<0.01$) compared with patients with adult-onset craniopharyngioma. Visual field defects (85% vs 59%, $P<0.01$), cognitive impairment (16% vs 3%, $P=0.02$), overweight (39% vs 16%, $P<0.01$) and secondary hypothyroidism (56% vs 32%, $P<0.01$) were significantly more common in patients with adult- compared with childhood-onset craniopharyngioma.

Craniopharyngioma characteristics at diagnosis

Tumour characteristics at diagnosis are depicted in Table 1. Tumour consistency was significantly different between patients with childhood- and adult-onset craniopharyngioma. Bonferroni-corrected *post hoc* analyses revealed a significantly higher number of multicystic craniopharyngiomas in patients with childhood- compared with adult-onset disease (45% vs 21%; $P=0.02$). Hydrocephalus, as well as hypothalamic and/or third ventricle involvement were also significantly more common in patients with childhood- compared with adult-onset craniopharyngioma (40% vs 18%, $P<0.01$; 66% vs 42%, $P=0.01$). Patient and tumour characteristics were not significantly different between different initial craniopharyngioma treatment approaches (Table 2).

Craniopharyngioma treatment

In the patients who were initially treated with neurosurgical excision, the neurosurgical approach

was transsphenoidal in 35 patients (39%), subfrontal in 31 patients (35%), pterional in 20 patients (23%), transcallosal in two patients (2%) and supra-orbital in one patient (1%). In five patients (5%) data regarding the neurosurgical approach were missing. There were no significant differences in the neurosurgical approaches used between patients treated with gross total resection, subtotal resection without radiotherapy and subtotal resection with radiotherapy. Initial craniopharyngioma treatment approaches, as well as neurosurgical approaches were not significantly different between patients with childhood- and adult-onset craniopharyngioma. In the patients who initially received radiotherapy, conventional external beam radiotherapy was applied to eight patients and stereotactic radiotherapy to 16 patients. In four patients, detailed information on the type of radiotherapy was missing. In the patients who were initially treated with radiotherapy, the median cumulative radiation dose was 54 Gy (interquartile range: 54–54 Gy); delivered in a median 30 fractions (interquartile range: 30–30 fractions). The median duration between neurosurgery and radiotherapy was two months (interquartile range: 1–6 months).

In our institution, initial craniopharyngioma treatment changed over time (Fig. 1). The use of gross total resection declined from 22% during 1980–1989 to 12% in ≥ 2010 . Meanwhile, the use of subtotal resection (with or without radiotherapy) increased from 30% during 1980–1989 to 71% in ≥ 2010 . $^{90}\text{Yttrium}$ brachytherapy was predominantly used during 1980–1989.

Long-term health conditions

Long-term health conditions in patients with craniopharyngioma are shown in Table 3. Pituitary hormone deficiencies, visual disturbances and obesity were the most common long-term health effects and affected 98, 75 and 56% of the patients respectively. Hypogonadotropic hypogonadism was the most common pituitary hormone deficiency and was found in 92% of the patients. Diabetes insipidus was diagnosed in 61% of the patients. Five patients demonstrated blindness (four after initial treatment with subtotal resection; one after initial treatment with $^{90}\text{Yttrium}$ brachytherapy). Severe neurological deficits (i.e. compromising independent daily living) affected 11 patients. In three patients, severe neurological deficits were directly related to the craniopharyngioma itself. One patient developed radiation encephalopathy six years after conventional external beam radiotherapy at an age of 41 years. Three

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Table 1 Baseline characteristics, presenting symptoms, and tumour characteristics at diagnosis. Data are presented as *n* (%).

Baseline characteristics	All craniopharyngiomas	Childhood-onset	Adult-onset	P-value*
<i>n</i>	128	63	65	
Male	57 (45)	25 (40)	32 (49)	0.28
Female	71 (56)	38 (60)	33 (51)	
Age (year) at presentation, median (IQR)	19 (8–42)	8 (5–12)	41 (29–55)	<0.01
Presenting symptoms				
Headaches	83 (68)	42 (71)	41 (65)	0.47
Visual acuity disorders	73 (73)	33 (72)	40 (74)	0.79
Visual field defects	72 (74)	23 (59)	49 (85)	<0.01
Epilepsy	7 (6)	6 (10)	1 (2)	0.06
Neurological deficits	42 (34)	25 (42)	17 (27)	0.07
Altered level of consciousness	26 (21)	15 (25)	11 (18)	0.28
Cognitive impairment	12 (10)	2 (3)	10 (16)	0.02
Behavioural changes	15 (12)	8 (14)	7 (11)	0.68
History of weight change				0.14
Increase	13 (11)	3 (5)	10 (16)	
Decrease	19 (16)	9 (15)	10 (16)	
Weight status (BMI (kg/m ²))				
Underweight (<18.5)	10 (10)	8 (16)	2 (4)	0.09
Normal weight (18.5–24.9)	51 (51)	31 (61)	20 (41)	0.05
Overweight (25.0–29.9)	27 (27)	8 (16)	19 (39)	<0.01
Class I obesity (30.0–34.9)	7 (7)	2 (4)	5 (10)	0.26
Class II obesity (35.0–39.9)	2 (2)	0 (0)	2 (4)	0.24
Class III obesity (≥40.0)	3 (3)	2 (4)	1 (2)	1.00
Class I–III obesity (≥30.0)	12 (12)	4 (8)	8 (16)	0.19
Pituitary hormone deficiencies	87 (71)	40 (68)	47 (73)	0.49
GH	48 (40)	31 (53)	17 (27)	<0.01
FSH/LH	49 (60)	10 (56)	39 (61)	0.68
ACTH	42 (34)	17 (28)	25 (39)	0.21
TSH	54 (44)	19 (32)	35 (56)	<0.01
ADH	8 (7)	4 (7)	4 (6)	1.00
Anterior PH	17 (14)	10 (17)	7 (12)	0.39
Complete PH	4 (3)	2 (3)	2 (3)	1.00
Tumour characteristics				
Localization				0.87
Intrasellar	5 (4)	3 (5)	2 (3)	
Suprasellar	48 (39)	23 (38)	25 (40)	
Intra-/suprasellar	70 (57)	34 (57)	36 (57)	
Consistency				0.02
Unicystic	71 (61)	29 (52)	42 (69)	
Multicystic	38 (33)	25 (45)	13 (21)	
Solid	8 (7)	2 (4)	6 (10)	
Presence of hydrocephalus	36 (29)	25 (40)	11 (18)	<0.01
Hypothalamic and/or third ventricle involvement	60 (53)	35 (66)	25 (42)	0.01
Brain stem compression	16 (14)	6 (11)	10 (17)	0.39

Data regarding headaches, epilepsy, neurological deficits, altered level of consciousness, cognitive impairment, behavioural changes and weight change were missing in 6 patients. Data regarding visual acuity disorders and visual field defects were missing in 28 and 31 patients respectively. Weight status could not be determined in 28 patients. Data regarding pituitary hormone deficiencies were missing in 8 patients (growth hormone (GH) in 7 patients, follicle stimulating hormone/luteinizing hormone (FSH/LH) in 4 patients, adrenocorticotrophic hormone (ACTH) in 4 patients, thyroid stimulating hormone (TSH) in 5 patients, antidiuretic hormone (ADH) in 4 patients, and anterior and complete panhypopituitarism (PH) in 8 patients). Also, 42 patients were too young to reliably assess gonadal function (girls <14 years of age; boys <15 years of age). Data regarding initial craniopharyngioma localization, consistency, hydrocephalus, hypothalamic and/or third ventricle involvement, and brain stem compression were missing in 5, 11, 3, 15 and 14 patients respectively.

BMI, body mass index; IQR, interquartile range.

*Childhood- vs adult-onset

patients suffered from radionecrosis related to leakage of the installed radio-isotope a median 15 months after ⁹⁰Yttrium brachytherapy at a median age of 54 years. In four patients, cerebrovascular events caused severe

neurological dysfunction a median seven months after initial craniopharyngioma treatment at a median age of 27 years. This latter group included one child who experienced a cerebral infarction of the entire left

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Table 2 Patient characteristics and tumour characteristics at diagnosis according to initial craniopharyngioma treatment. Data are presented as *n* (%).

Baseline characteristics	GTR	STR w/o RTx	STR with RTx	Cyst aspiration	⁹⁰ Yttrium	P-value
<i>n</i>	25	44	25	8	21	
Male	9 (36)	19 (43)	11 (44)	3 (38)	12 (57)	0.69
Female	16 (64)	25 (57)	14 (56)	5 (63)	9 (43)	
Age (year) at presentation, median (IQR)	15 (8–37)	26 (9–41)	26 (15–46)	13 (5–71)	11 (6–45)	0.38
Tumour characteristics						
Localization						0.84
Intrasellar	1 (4)	1 (2)	1 (4)	0 (0)	1 (5)	
Suprasellar	9 (39)	14 (33)	9 (38)	5 (63)	10 (48)	
Intra-/suprasellar	13 (57)	28 (65)	14 (58)	3 (38)	10 (48)	
Consistency						0.81
Unicystic	15 (65)	23 (58)	15 (65)	5 (63)	13 (65)	
Multicystic	7 (30)	14 (35)	6 (26)	3 (38)	7 (35)	
Solid	1 (4)	3 (8)	2 (9)	0 (0)	0 (0)	
Presence of hydrocephalus	6 (25)	10 (23)	5 (21)	5 (63)	7 (33)	0.18
Hypothalamic and/or third ventricle involvement	11 (48)	20 (50)	15 (68)	6 (75)	7 (41)	0.28
Brain stem compression	2 (9)	4 (10)	4 (17)	1 (13)	4 (24)	0.65

Data regarding initial craniopharyngioma localization, consistency, hydrocephalus, hypothalamic and/or third ventricle involvement, and brain stem compression were missing in 4, 9, 3, 13 and 12 patients respectively.

IQR, interquartile range; ⁹⁰Yttrium, ⁹⁰Yttrium brachytherapy; GTR, gross total resection; RTx, radiotherapy; STR, subtotal resection; w/o, without.

hemisphere without a known cause approximately two years after craniopharyngioma resection.

Long-term health conditions according to initial craniopharyngioma treatment are shown in Table 4. Initial craniopharyngioma treatment with gross total resection, subtotal resection with or without radiotherapy, cyst aspiration and ⁹⁰Yttrium brachytherapy resulted in a similar pattern of long-term health effects. Long-term health conditions in patients with childhood- compared with adult-onset craniopharyngioma are shown in Table 3. Patients with childhood-onset craniopharyngioma demonstrated significantly more growth hormone deficiency (93% vs 68%, $P<0.01$), diabetes insipidus (79%

vs 43%, $P<0.01$), anterior panhypopituitarism (79% vs 61%, $P=0.03$), complete panhypopituitarism (66% vs 34%, $P<0.01$), morbid obesity (24% vs 6%, $P<0.01$), epilepsy (32% vs 15%, $P=0.03$) and psychiatric conditions (56% vs 23%, $P<0.01$) compared with patients with adult-onset craniopharyngioma. Cardio- and cerebrovascular events were significantly more common in patients with adult- compared with childhood-onset craniopharyngioma (26% vs 5%, $P<0.01$).

Initial craniopharyngioma treatment in more recent decades resulted in significant reductions of morbid obesity (odds ratio (OR): 0.3, 95% confidence interval (CI): 0.12–0.86; $P=0.02$) and severe neurological deficits (OR: 0.4, 95% CI: 0.21–0.97; $P=0.04$) after adjustment for follow-up duration. In addition, a prolonged follow-up duration after craniopharyngioma presentation was associated with a significantly lower risk of severe neurological deficits after adjustment for treatment decade (OR: 0.9, 95% CI: 0.81–0.98; $P=0.02$).

Survival

Overall and recurrence-/progression-free survival after initial craniopharyngioma treatment are shown in Figs 2 and 3. Overall survival was 93, 85 and 77% at 5, 10 and 20 years of follow-up. Recurrence-/progression-free survival was 90, 74 and 52% at 5, 10 and 20 years of follow-up. Although overall survival was comparable after initial craniopharyngioma treatment with gross total resection, subtotal resection with or without radiotherapy,

Figure 1

Initial craniopharyngioma treatment per decade. %, percentage; ⁹⁰Yttrium, ⁹⁰Yttrium brachytherapy; GTR, gross total resection; RTx, radiotherapy; STR, subtotal resection; w/o, without.

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Table 3 Long-term health conditions in patients with craniopharyngioma.

	All craniopharyngiomas	Childhood-onset	Adult-onset	P-value**
<i>n</i>	128	63	65	
Follow-up (years) since presentation, median (IQR)	13 (5–23)	14 (5–23)	11 (6–23)	0.81
Age (years) at follow-up, median (IQR)	37 (21–54)	22 (15–31)	54 (44–70)	<0.01
Visual acuity disorders	71 (63)	34 (63)	37 (64)	0.93
Visual field defects	65 (66)	31 (66)	34 (65)	0.95
Epilepsy	30 (23)	20 (32)	10 (15)	0.03
Neurological deficits:	30 (23)	16 (25)	14 (22)	0.61
Mild	19 (15)	10 (16)	9 (14)	0.75
Severe	11 (9)	6 (10)	5 (8)	0.71
Cognitive impairment	36 (28)	22 (35)	14 (22)	0.09
Behavioural changes	24 (19)	12 (19)	12 (19)	0.93
Psychiatric conditions	50 (39)	35 (56)	15 (23)	<0.01
Weight status (BMI (kg/m ²))				
Underweight (<18.5)	4 (4)	4 (7)	0 (0)	0.12
Normal weight (18.5–24.9)	18 (16)	7 (12)	11 (21)	0.22
Overweight (25.0–29.9)	27 (24)	10 (17)	17 (32)	0.07
Class I obesity (30.0–34.9)	34 (31)	18 (31)	16 (30)	0.92
Class II obesity (35.0–39.9)	11 (10)	5 (9)	6 (11)	0.63
Class III obesity (≥40.0)	17 (15)	14 (24)	3 (6)	<0.01
Class I–III obesity (≥30.0)	62 (56)	37 (64)	25 (47)	0.08
Obstructive sleep apnoea	11 (9)	7 (11)	4 (6)	0.32
Pituitary hormone deficiencies:	125 (98)	61 (97)	64 (99)	0.62
GH	99 (81)	57 (93)	42 (68)	<0.01
FSH/LH	110 (92)	49 (91)	61 (94)	0.73
ACTH	111 (87)	54 (86)	57 (88)	0.74
TSH	116 (91)	58 (92)	58 (91)	0.77
ADH	78 (61)	50 (79)	28 (43)	<0.01
Anterior PH	85 (70)	48 (79)	37 (61)	0.03
Complete PH	63 (50)	41 (66)	22 (34)	<0.01
Secondary neoplasms*	22 (17)	7 (11)	15 (23)	0.07
Cardio- and/or cerebrovascular events	20 (16)	3 (5)	17 (26)	<0.01

Data regarding visual acuity disorders and visual field defects were missing in 16 and 29 patients respectively. Weight status could not be determined in 17 patients. Data regarding pituitary hormone deficiencies were missing in 6 patients (GH in 5 patients, FSH/LH in 1 patient, TSH in 1 patient, anterior PH in 6 patients, and complete PH in 1 patient). Also, 8 patients were too young to reliably assess gonadal function.

*Secondary neoplasms included meningioma ($n=2$), prostate cancer ($n=2$), breast cancer ($n=2$), arachnoid cyst ($n=2$), thyroglossal duct cyst ($n=1$), fibroadenoma ($n=2$), cavernous sinus schwannoma ($n=1$), growth hormone-producing pituitary adenoma ($n=1$), pineal gland cyst ($n=1$), pancreatic cancer ($n=1$), lung cancer ($n=1$), mesothelioma ($n=1$), bladder cancer ($n=1$), ovarian cancer ($n=1$), cervical cancer ($n=1$), calcifying odontogenic cyst ($n=1$), osteoma of the skull ($n=1$), haemangioma ($n=1$), Hodgkin lymphoma ($n=1$) and neuro-endocrine tumour of the appendix ($n=1$).

**Childhood vs adult-onset

BMI, body mass index; IQR, interquartile range.

cyst aspiration and ⁹⁰Yttrium brachytherapy, recurrence-/progression-free survival was not ($P=0.03$). Bonferroni-corrected *post hoc* analyses revealed a significantly lower recurrence-/progression-free survival after initial craniopharyngioma treatment with cyst aspiration compared with the other treatment approaches ($P=0.01$). Overall and recurrence-/progression-free survival were similar in patients with childhood- and adult-onset craniopharyngioma. Patients with craniopharyngioma recurrence/progression experienced a significantly lower overall survival compared with patients without craniopharyngioma recurrence/progression ($P<0.01$). Initial craniopharyngioma treatment in more recent decades resulted in similar overall survival ($P=0.50$ for

trend) and lower recurrence-/progression-free survival ($P<0.01$ for trend). Overall survival was also similar over time in the subgroup of patients with craniopharyngioma recurrence/progression ($P=0.46$ for trend).

In our study, 22 patients (17%) died during follow-up. In five patients (23%) the cause of death was directly related to the craniopharyngioma itself (tumour invading vital brain structures ($n=4$), brain herniation ($n=1$)). Eleven patients (50%) died of causes not directly related to the craniopharyngioma itself (infection ($n=4$), cardiac arrest ($n=2$), secondary malignancies ($n=3$), cerebrovascular infarction ($n=1$), radiation encephalopathy ($n=1$)). The cause of death was unknown in six patients (27%). Deaths directly related to the craniopharyngioma itself

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Table 4 Long-term health conditions according to initial craniopharyngioma treatment. Data represented as *n* (%).

	GTR	STR w/o RTx	STR with RTx	Cyst aspiration	⁹⁰ Yttrium	P-value
<i>n</i>	25	44	25	8	21	0.13
Follow-up (years), median (IQR)	14 (6–21)	9 (5–23)	10 (6–14)	12 (2–24)	22 (9–29)	0.13
Age (years) at follow-up, median (IQR)	30 (18–51)	42 (21–60)	40 (21–65)	37 (18–74)	35 (28–56)	0.72
Visual acuity disorders	10 (50)	24 (63)	14 (58)	5 (71)	16 (84)	0.20
Visual field defects	12 (67)	19 (61)	11 (52)	5 (71)	17 (94)	0.07
Epilepsy	6 (24)	10 (23)	3 (12)	2 (25)	8 (38)	0.36
Neurological deficits	6 (24)	8 (18)	5 (20)	1 (13)	9 (43)	0.25
Mild	3 (12)	6 (14)	3 (12)	1 (13)	5 (24)	0.81
Severe	3 (12)	2 (5)	2 (8)	0 (0)	4 (19)	0.28
Cognitive impairment	11 (44)	7 (16)	9 (36)	2 (25)	7 (33)	0.11
Behavioural changes	4 (16)	9 (21)	7 (28)	2 (25)	2 (10)	0.56
Psychiatric conditions	8 (32)	18 (41)	9 (36)	5 (63)	8 (38)	0.65
Weight status (BMI (kg/m ²))						
Underweight (<18.5)	0 (0)	3 (8)	1 (4)	0 (0)	0 (0)	0.28
Normal weight (18.5–24.9)	5 (22)	6 (16)	4 (17)	1 (13)	2 (13)	0.95
Overweight (25.0–29.9)	7 (30)	10 (27)	4 (17)	2 (25)	3 (19)	0.82
Class I obesity (30.0–34.9)	5 (22)	11 (30)	8 (35)	2 (25)	6 (38)	0.82
Class II obesity (35.0–39.9)	2 (9)	2 (5)	3 (13)	2 (25)	2 (13)	0.58
Class III obesity (≥40.0)	4 (17)	5 (14)	3 (13)	1 (13)	3 (19)	0.98
Class I–III obesity (≥30.0)	11 (48)	18 (49)	14 (61)	5 (63)	11 (69)	0.58
Obstructive sleep apnoea	3 (12)	5 (11)	1 (4)	1 (13)	1 (5)	0.71
Pituitary hormone deficiencies:	23 (92)	44 (100)	25 (100)	7 (88)	21 (100)	0.08
GH	19 (79)	34 (77)	20 (80)	5 (63)	17 (94)	0.33
FSH/LH	21 (88)	38 (95)	22 (92)	6 (86)	18 (95)	0.46
ACTH	22 (88)	40 (91)	22 (88)	6 (75)	17 (81)	0.71
TSH	22 (88)	41 (95)	22 (88)	6 (75)	20 (95)	0.41
ADH	17 (68)	30 (68)	13 (52)	4 (50)	10 (48)	0.38
Anterior PH	18 (75)	29 (67)	19 (76)	4 (50)	12 (67)	0.66
Complete PH	16 (64)	21 (48)	12 (48)	3 (38)	8 (40)	0.49
Secondary neoplasms	2 (8)	11 (25)	6 (24)	1 (13)	1 (5)	0.12
Cardio- and/or cerebrovascular events	2 (8)	8 (18)	4 (16)	2 (25)	4 (19)	0.71

Data regarding visual acuity disorders and visual field defects were missing in 15 and 28 patients respectively. Weight status could not be determined in 16 patients. Data regarding pituitary hormone deficiencies were missing in 5 patients (GH in 4 patients, FSH/LH in 1 patient, TSH in 1 patient, anterior PH in 5 patients, and complete PH in 1 patient). Also 8 patients were too young to reliably assess gonadal function.

IQR, interquartile range; ⁹⁰Yttrium, ⁹⁰Yttrium brachytherapy; BMI, body mass index; GTR, gross total resection; RTx, radiotherapy; STR, subtotal resection; w/o, without.

and deaths not directly related to the craniopharyngioma itself occurred with similar frequencies after initial craniopharyngioma treatment with gross total resection, subtotal resection with or without radiotherapy, cyst aspiration and ⁹⁰Yttrium brachytherapy ($P=0.90$), as well as in patients with childhood- and adult-onset disease ($P=0.28$).

Discussion

In this large single-centre study of patients with craniopharyngioma treated from 1980 onwards, we cross-sectionally analysed retrospectively collected data on a full spectrum of long-term health conditions. After a median follow-up of 13 years since presentation, we observed a similar pattern of long-term health effects after initial craniopharyngioma treatment with gross total

resection, subtotal resection with or without radiotherapy, cyst aspiration and ⁹⁰Yttrium brachytherapy. In general, long-term health conditions were more frequent in patients with childhood- compared with adult-onset craniopharyngioma.

Pituitary hormone deficiencies, visual disturbances and obesity were the most frequently observed long-term health conditions in our study. This is in concordance with other studies that reported prevalence rates of 78–100% for pituitary hormone deficiencies, 49–87% for visual disturbances and 27–57% for obesity (10, 20, 22, 23, 26, 28, 30, 32). Notably, we observed a relatively high frequency of obstructive sleep apnoea (i.e. 9%) in patients with craniopharyngioma. This is considerably higher than the prevalence of obstructive sleep apnoea in the Dutch general population, which is estimated to be 1–4% (38). Since only patients with suspected sleep disordered

Figure 2

Overall survival in patients with craniopharyngioma. (A) All patients. (B) According to initial craniopharyngioma treatment. (C) Patients with childhood- and adult-onset craniopharyngioma. (D) According to recurrence/progression status. ⁹⁰Yttrium, ⁹⁰Yttrium brachytherapy; GTR, gross total resection; RTx, radiotherapy; STR, subtotal resection; w/o, without.

breathing were evaluated for obstructive sleep apnoea in our study, the observed frequency of 9% may even be an underestimation of the real prevalence of obstructive sleep apnoea in patients with craniopharyngioma. Only a few other studies compared long-term health conditions in patients with craniopharyngioma according to initial treatment approach (17, 35, 36, 37). In concordance with our results, these studies observed no important differences in long-term health effects after different initial craniopharyngioma treatment approaches. Lo *et al.* only observed a higher frequency of diabetes insipidus after initial craniopharyngioma treatment with neurosurgery compared with craniopharyngioma treatment without neurosurgery in 123 patients after a median follow-up of 9 years (35). Karavitaki *et al.* only observed more visual field defects after initial craniopharyngioma treatment with subtotal resection without radiotherapy compared with craniopharyngioma treatment with gross total resection or subtotal resection with radiotherapy in 121 patients after a mean follow-up of 9 years (36). Schoenfeld *et al.* only observed a higher rate of diabetes insipidus and panhypopituitarism after initial craniopharyngioma treatment with gross total resection compared with subtotal resection with or without radiotherapy in 122 patients after a median follow-up of 5 years (17). Merchant *et al.* only observed more diabetes insipidus and less hypogonadotropic hypogonadism after initial craniopharyngioma treatment with gross total resection

compared with subtotal resection with radiotherapy in 30 patients after a median follow-up of 6 years (37).

In our study, long-term health conditions seemed to occur more frequently in patients with childhood-compared with adult-onset craniopharyngioma. This may be explained by differences in tumour characteristics between patients with childhood- and adult-onset craniopharyngioma already present at diagnosis. In our study, patients with childhood-onset craniopharyngioma presented more often with multicystic tumours, as well as tumours associated with hydrocephalus and hypothalamic and/or third ventricle involvement compared with patients with adult-onset craniopharyngioma. In contrast, we observed significantly more cardio- and cerebrovascular events in patients with adult- compared with childhood-onset disease. This may be due to the significantly older age at follow-up of patients with adult-onset craniopharyngioma. Aging has been established as an important risk factor for cardio- and cerebrovascular disease (39). Several other studies compared long-term health conditions between patients with childhood- and adult-onset craniopharyngioma (28, 30, 36). In concordance with our results, Gautier *et al.* observed a significantly higher prevalence of diabetes insipidus and panhypopituitarism in patients with childhood-compared with adult-onset disease in a cohort of 171 patients derived from two academic centres in France after a median follow-up of 12 years (30). In contrast,

Figure 3

Recurrence-/progression-free survival in patients with craniopharyngioma. (A) All patients. (B) According to initial craniopharyngioma treatment. (C) Patients with childhood- and adult-onset craniopharyngioma. ⁹⁰Yttrium, ⁹⁰Yttrium brachytherapy; GTR, gross total resection; RTx, radiotherapy; STR, subtotal resection; w/o, without.

Kendall-Taylor *et al.* observed a significantly higher frequency of obesity in patients with adult- compared with childhood-onset craniopharyngioma. In their study, which included 393 growth hormone-deficient patients from the KIMS (Pfizer International Metabolic Database) who were followed for a mean 17 years, frequencies of any pituitary hormone deficiency and panhypopituitarism were similar between patients with childhood- and adult-onset disease (28). The aforementioned study by

Karavitaki *et al.* did not observe any significant differences in long-term health conditions between patients with childhood- and adult-onset craniopharyngioma, except for complete dependency for activities of daily living, which was more common in patients with adult-onset craniopharyngioma (36).

We observed 10-year overall and recurrence-/progression-free survival rates after initial craniopharyngioma treatment of 85% and 74% respectively. This is comparable to other studies in patients with craniopharyngioma that reported 10-year overall and recurrence-/progression-free survival rates between 40–95% and 44–76% respectively (10, 21, 22, 23, 24, 25). In our study, overall survival was similar after initial craniopharyngioma treatment with gross total resection, subtotal resection with or without radiotherapy, cyst aspiration and ⁹⁰Yttrium brachytherapy. However, recurrence-/progression-free survival was significantly lower after initial craniopharyngioma treatment with cyst aspiration compared with the other therapeutic approaches. Two other studies also investigated overall and recurrence-/progression-free survival in patients with craniopharyngioma according to initial treatment approach (34, 36). The aforementioned study by Karavitaki *et al.* observed similar overall survival after initial craniopharyngioma treatment with gross total resection and subtotal resection with or without radiotherapy. However, recurrence-/progression-free survival was significantly lower after initial craniopharyngioma treatment with subtotal resection without radiotherapy compared with gross total resection or subtotal resection with radiotherapy (36). A recent study by Rao *et al.* investigated 5-year overall survival in 697 patients with craniopharyngioma registered in the United States National Cancer Database. Overall survival was significantly lower after subtotal resection without radiotherapy compared with gross total resection or subtotal resection with radiotherapy (34). In our study, overall and recurrence-/progression-free survival were comparable in patients with childhood- and adult-onset craniopharyngioma. Other studies observed similar results (24, 30, 36). However, the aforementioned study by Rao *et al.* observed significantly lower overall survival in patients with adult- compared with childhood-onset craniopharyngioma (34). Interestingly, patients with craniopharyngioma seem to have an increased mortality risk compared with patients with other pituitary diseases (21). This might be related to long-term health conditions caused by tumour and treatment (e.g. hypopituitarism and hypothalamic dysfunction),

as well as to the locally aggressive behaviour of craniopharyngiomas and their tendency to recur after treatment (21, 22).

In our institution, initial craniopharyngioma treatment became less aggressive over time. This is in concordance with other studies (4, 20). We observed significantly lower risks of morbid obesity and severe neurological deficits after initial craniopharyngioma treatment in more recent decades. In contrast, we observed a significantly higher risk of recurrence/progression in patients treated for craniopharyngioma in more recent decades.

Strengths of our study include the full spectrum of long-term health conditions investigated, as well as the relatively large number of patients treated with ⁹⁰Yttrium brachytherapy assessed. Brachytherapy was first introduced as a treatment for craniopharyngioma in 1952 by Leksell and Liden, and involves the minimally-invasive stereotactic application of beta-emitting isotopes in craniopharyngioma cysts (40). Subsequent radiation-induced destruction of epithelial cyst lining results in cyst shrinkage (41). Due to the short half-value depth of ⁹⁰Yttrium in soft tissue, ⁹⁰Yttrium brachytherapy is not effective for solid craniopharyngiomas (42). Only a few other studies investigated long-term health conditions after craniopharyngioma treatment with ⁹⁰Yttrium brachytherapy (42, 43, 44). These studies reported somewhat lower frequencies of long-term health effects compared with our study (55–90% for pituitary hormone deficiencies, 61–90% for visual disturbances and 51% for obesity). This may be explained by a longer follow-up duration after ⁹⁰Yttrium brachytherapy in our study (22 years vs 3–12 years in the other studies). Besides these strengths, some limitations should be considered when interpreting the results of our study. The retrospective nature of data collection may predispose to selection bias and missing data. However, due to the rarity of craniopharyngioma and the prolonged follow-up duration required to adequately study long-term health conditions, it seems unlikely that prospective observational studies with an adequate follow-up duration and a sufficient number of patients will become available in the near future. In addition, neuroimaging techniques were less sensitive earlier compared with more recent decades. This may have biased the assessment of the degree of craniopharyngioma resection, especially during earlier decades. Furthermore, our results on long-term neurocognitive and neuropsychological sequelae should be interpreted with caution, as cognitive impairments

and behavioural changes were considered present if documented in the patient files and have not been formally tested. Moreover, we were unable to compare long-term health conditions according to histological subtype of craniopharyngioma (i.e. adamantinomatous or papillary), since these data were only available in a minority of patients.

In conclusion, our study demonstrates that despite encouraging survival rates, long-term health conditions are frequent in patients with craniopharyngioma. Initial gross total resection, subtotal resection with or without radiotherapy, cyst aspiration and ⁹⁰Yttrium brachytherapy result in comparable long-term health effects. Patients with childhood-onset craniopharyngioma are generally more affected by long-term health conditions than patients with adult-onset disease. Craniopharyngioma should be regarded as a chronic condition requiring multidisciplinary management, both at diagnosis and during follow-up. Due to the high frequency of endocrine disorders, endocrinologists should play a pivotal role in the primary and follow-up care of patients with craniopharyngioma. Future studies on craniopharyngioma should focus on modifiable risk factors for long-term health conditions, as well as on therapeutic strategies that aim to reduce the long-term tumour- and treatment-related morbidity.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Acknowledgements

The authors would like to thank the physicians involved in the treatment and follow-up care of our patients.

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Received 19 January 2017

Revised version received 16 March 2017

Accepted 21 March 2017