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Background. Quality of life (QoL) and long-term prognosis are frequently, and often severely, impaired in craniopharyngioma (CP) patients. Knowledge of risk factors for long-term outcome is important for optimization of treatment.

Methods. Overall survival (OS) and progression-free survival (PFS), body mass index (BMI), neuropsychological status (EORTCQLQ-C30, MFI-20), and psychosocial status were analyzed in 261 patients with childhood-onset CP diagnosed before 2000 and longitudinally observed in HIT-Endo.

Results. Twenty-year OS was lower ($P = .006$) in CP with hypothalamic involvement (HI) ($n = 132$; 0.84 ± 0.04) when compared with CP without HI ($n = 82$; 0.95 ± 0.04). OS was not related to degree of resection, sex, age at diagnosis, or year of diagnosis (before/after 1990). PFS ($n = 168$; 0.58 ± 0.05) was lower in younger patients (<5y at diagnosis) ($n = 30$; 0.39 ± 0.10) compared with patients aged 5–10 years ($n = 66$; 0.52 ± 0.08) and older than 10 years ($n = 72$; 0.77 ± 0.06) at diagnosis. PFS was not associated with HI, degree of resection, or sex. HI led to severe weight gain during the first 8–12 years of follow-up (median BMI increase: +4.59SD) compared with no HI (median increase: +1.20SD) ($P = .00$). During >12 years of follow-up, patients with HI presented no further increase in BMI. QoL in CP patients with HI was impaired by obesity, physical fatigue, reduced motivation, dyspnea, diarrhea, and nonoptimal psychosocial development.

Conclusions. OS and QoL are impaired by HI in long-term survivors of CP. HI is associated with severe obesity, which plateaus after 12 years. OS/PFS are not related to degree of resection, but gross-total resection should be avoided in cases of HI to prevent further hypothalamic damage, which exacerbates sequelae.

Keywords: craniopharyngioma, hypothalamus, obesity, quality of life, pediatrics.

Craniopharyngiomas (CPs) are rare sellar malformations with low histological grade. Between 30% and 50% of all cases are diagnosed in children and adolescents.[1,2] Childhood-onset CP represents 1.2%–4% of all childhood intracranial tumors, making it the most common pituitary mass in childhood. Thus far, the preferred surgical treatment of CP has been radical resection. However, anatomical involvement and/or surgical lesions of posterior hypothalamic areas can result in serious sequelae compromising patient quality of life (QoL) such as hypothalamic obesity, psychopathological symptoms, and/or cognitive problems.[3–6] Therefore, the recommended therapy for patients with hypothalamic involvement (HI) is a strategy of limited hypothalamus-sparing surgical followed by local irradiation.[2,3]

Despite today's knowledge concerning pathogenic mechanisms in hypothalamic obesity and the trend towards hypothalamus-sparing surgical approaches, no treatment of hypothalamic obesity has proven to be effective thus far.[5] In the current study, we analyzed survival rates, weight development, neuropsychological status, psychosocial status, and QoL in a large cohort of long-term survivors of childhood-onset CP.

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Participants and Methods

Patients

For this study, anamneses of 280 patients with childhood-onset CP, recruited in a multinational CP registry and prospectively evaluated in the multicenter trial HIT Endo, were longitudinally analyzed.[7] The HIT Endo data include results of physical examination, anthropometric measurements, and evaluation of patient records for imaging results, clinical manifestations, history, operative strategies, and irradiation. The histological diagnosis of CP was confirmed by reference assessment in all cases. HI was assessed by MRI and/or microscopic inspection during surgery. HI was defined as involvement of hypothalamic structures either by tumor growth into the hypothalamus or displacement of hypothalamic structures by the tumor. Tumor size was calculated using the maximal tumor diameters in 2 dimensions based on the results of CT or MRI.

For long-term survival rates, we were able to analyze 261 (93%) cases.[7] After a minimum of 10 years follow-up, 3 questionnaires were sent out to the 165 patients for whom we had current postal addresses, to collect data on current weight and height, mental and physical fatigue, and psychosocial status. One-hundred eight (65%) of the 165 patients answered the questionnaires.

The study was approved by the local standing committee on ethical practice, and written parental and/or patient consent was obtained for all participants.

Body Mass Index

Body composition and the degree of obesity were evaluated by calculating the body mass standard deviation scores (BMI SDS) according to the references of Rolland-Cachera et al.[8]

Questionnaires

The EORTC QLQ-C30 is a questionnaire for assessing the health-related QoL in cancer patients.[9] The questionnaire consists of multi-item scales and single-item measures including 5 functional scales, 3 symptom scales, a global health status/QoL scale, and 6 single items. The scores of the scales and the single items are given as percentages. A score of 100% refers to the highest possible response to the particular item, and a score of 0% means no response at all. Functional scales and global health status are scored positively: the higher the percentage, the better the functioning and global health status of the patient. The symptom scales are scored negatively: the higher the percentage, the more symptoms are present.[9]

The MFI-20 questionnaire measures fatigue in 5 dimensions: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue. The domains of MFI-20 are measured by 20 questions that are scored by the participant on a scale from 1 to 5. These 5 domains can have a score from 4 to 20, expressed as a percentage: the higher the score, the more response for that domain and the more fatigue the participant claims to experience.[10]

A newly designed questionnaire created for the current study was used to assess the psychosocial status of the adult (aged >20y) long-term CP survivors of our cohort; it was sent to 42 CP participants and their 48 healthy adult siblings (who functioned as controls).

Statistical Analyses

Statistical analyses were performed using SPSS 19.0 (SPSS, INC.). For comparison of 2 independent groups for a continuous variable, the Mann-Whitney *U* test was used. For comparison of 2 related groups for a continuous variable, the Wilcoxon signed rank test was used. For comparison of different groups for categorical variables, the chi-square test was used. *P* values <.05 were chosen as being statistically significant. Overall survival (OS) and progression-free survival (PFS) rates were estimated by the Kaplan–Meier method.

Results

Long-term Outcomes in the Multicenter Study HIT Endo

Two-hundred eighty patients with childhood-onset CP diagnosed in the years between 1966 and 2000 were recruited in the multicenter study HIT Endo[7] and analyzed longitudinally. Long-term survival could be analyzed in 261 (93%) of these participants. The Kaplan–Meier curves showed a 20-year OS of 0.88 ± 0.03 (Fig. 1A) and a PFS of 0.58 ± 0.05 after 20 years (Fig. 1E). The comparison of participants after complete or incomplete resection showed no significant differences in terms of 20-year OS and PFS rates (Fig. 1B and F). In contrast, the comparison of participants with and without HI produced a significant difference in OS after 20 years (Fig. 1C). The 20-year OS rates were significantly higher in participants without HI (0.95 ± 0.04) than those with HI (0.84 ± 0.04) ($P = .006$), even though PFS rates were similar in participants with and without HI (Fig. 1G). Differences in terms of endocrine substitution and treating physicians were not detectable between HI and non-HI participants (see Supplementary material, Table 1). The main reasons for the 32 deaths in our cohort were acute adrenal insufficiency, tumor progression, and intracerebral vascular complications (see Supplementary material, Table 2).

We also analyzed OS with respect to age at diagnosis. Participants were grouped into ages younger than 5 years, 5–10 years, and older than 10 years at diagnosis. No significant differences could be detected. OS was 0.93 ± 0.02 in participants younger than aged 5 years, 0.88 ± 0.01 in participants between ages 5 and 10 years at diagnosis, and 0.88 ± 0.01 in patients older than aged 10 years at diagnosis. OS with respect to sex showed no significant differences (OS male: 0.90 ± 0.04 vs OS female: 0.87 ± 0.04). The analyses of PFS showed different results: PFS was lower in younger CP participants (aged <5y at diagnosis) ($n = 30$, 0.39 ± 0.10), compared with participants aged 5–10 years ($n = 66$, 0.52 ± 0.08) and those older than aged 10 years ($n = 72$, 0.77 ± 0.06). Differences in terms of OS and PFS among participants who did vs those who did not develop diabetes insipidus (DI)—identified by the need for DDAVP substitution after diagnosis—did not reach statistical difference (OS of patients with DI: 0.98 ± 0.02; OS of patients without DI: 0.85 ± 0.10; $P = .46$; PFS of patients with DI: 0.74 ± 0.05; PFS of patients without DI: 0.42 ± 0.21; $P = .604$). OS was similar for participants diagnosed before and after the year 1990. The OS for participants diagnosed before was

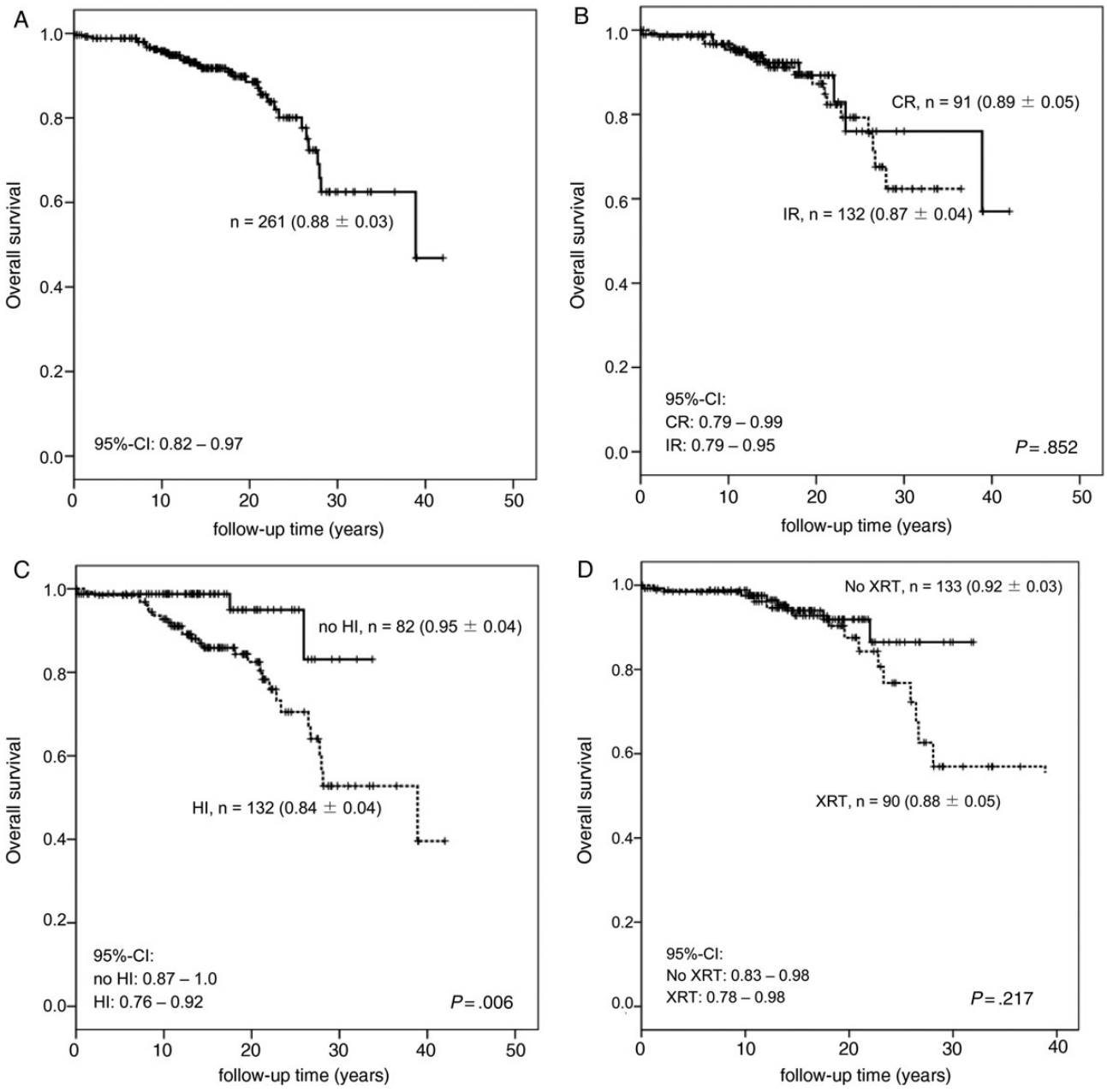

Fig. 1. Twenty-year overall survival (A) and 20-year progression-free survival (PFS) (E) of patients with childhood-onset craniopharyngioma recruited in HIT Endo. (B) depicts 20-year overall survival. (C) depicts 20-year overall survival. (D) depicts 20-year overall survival. (F) 20-year PFS related to the degree of surgical resection (CR = complete resection; IR = incomplete resection; as confirmed by neuroradiological reference assessment). (G) 20-year PFS related to hypothalamic involvement (HI). (H) 20-year PFS related to irradiation (XRT). Progression events before and after XRT are included in the analysis.

0.87 ± 0.04 versus 0.80 ± 0.08 for those diagnosed after 1990. The comparison of participants who received radiotherapy (XRT) versus those who did not showed no significant differences in the 20-year OS (Fig. 1D), but the 20-year PFS (Fig. 1H) indicated that XRT was a frequently chosen option for salvage therapy in the case of tumor progression. The questionnaires used to analyze the current weight and height, psychosocial status, and QoL of long-term survivors recruited in HIT Endo were sent to 165 participants at least 9.8 years after their diagnosis; 108 (65%) responded, and 57 (35%) did not. Those who responded versus those who did not respond were compared, and no differences were seen in terms of age, sex, BMI SDS, follow-up time, resection degree, and HI (data not shown).

The anthropometric parameters and psychosocial status of the 108 participants (50 males, 58 females) are outlined in Table 1. The median age at diagnosis was 8.1 years, and the average time interval between diagnosis and evaluation was 16.3 years (range: 9.8–36.4y). The median age at evaluation

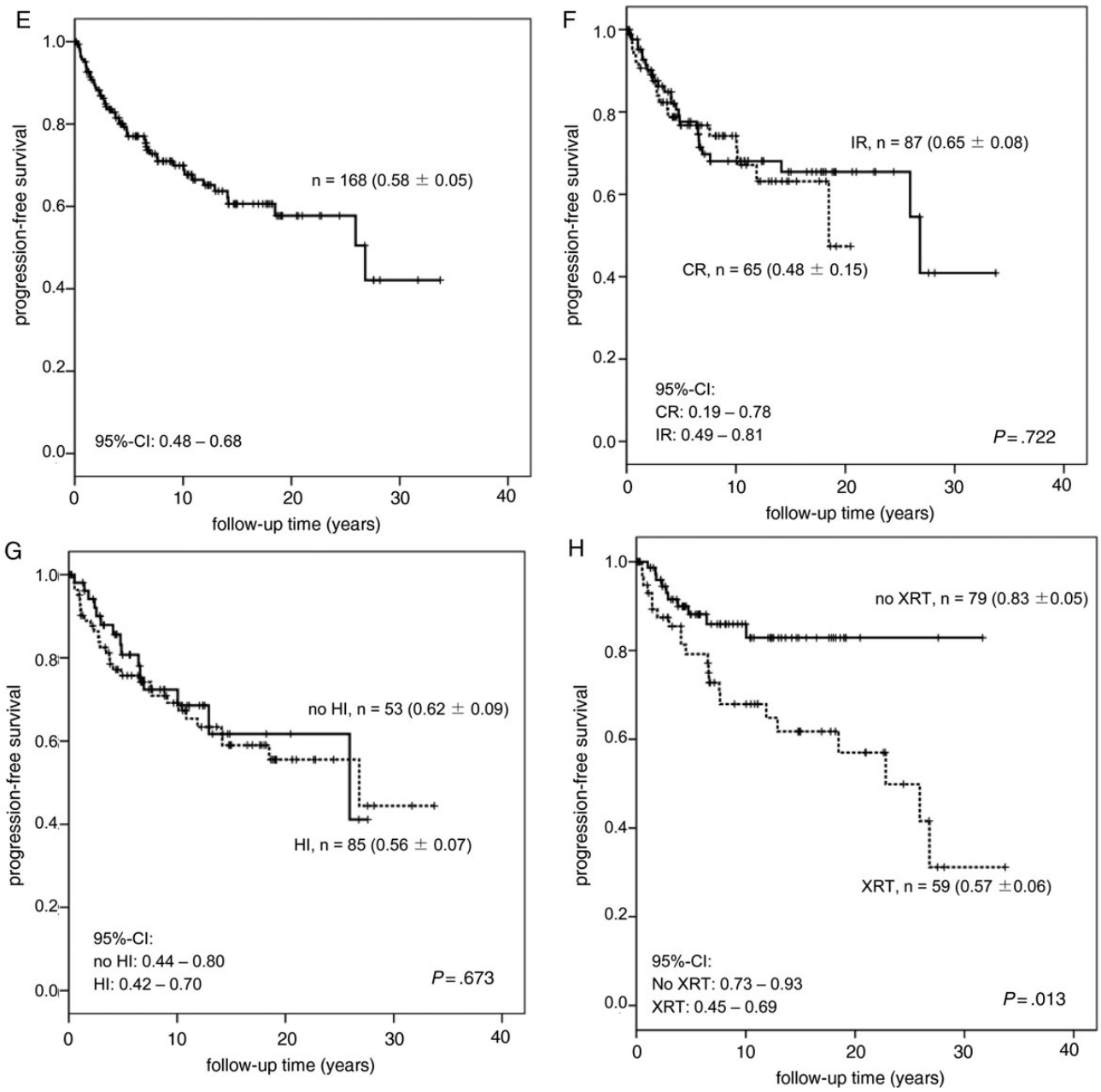

Fig. 1. Continued

was 24.8 years (range: 14.8–42.7y). The median BMI SDS at diagnosis was +0.70 SD (range: −2.7 to +7.0). The median BMI SDS at evaluation was +3.38 SD (range: −1.48 to +13.13 SD) ($P = .000$). All 108 participants underwent surgery: 44 (41%) a total resection, 54 (50%) had an incomplete resection, and the degree of resection was not specified for 10 (9%) participants. Fifty-two participants (48%) presented with proven HI, and 25 (23%) were without HI at the time of diagnosis. We compared characteristics of participants with and without proven HI. Because of limited quality of MRI diagnostics, the HI status of 31 participants (29%) could not be specified. Participants with proven HI at the time of diagnosis did not differ significantly with regard to sex, age at diagnosis, and BMI at diagnosis, but tumor size was higher in participants with HI when compared with participants without HI. Other parameters, such as initial symptoms in the participants' history, were equally distributed in both groups (Table 1).

Weight Development

We compared weight development in our cohort in relation to the presence of HI (a) at diagnosis, (b) during 8–12 years after diagnosis, and (c) after more than 12 years following diagnosis. The BMI SDS at the time of diagnosis was similar for both

Table 1. Patient characteristics of childhood-onset craniopharyngioma patients recruited in HIT Endo

Characteristics	All	Patients with Proven HI	Patients without HI
Number of patients, *n* (%)	108	52 (48)	25 (23)
Age at diagnosis, years, median (range)	8.1 (0.05–18.8)	7.6 (0.05–18.8)	10.1 (4.1–15.9)
Age at evaluation, years, median (range)	24.8 (14.8–42.7)	25.4 (15.1–42.7)	25.4 (15.3–42.5)
Follow-up time, years, median (range)	16.3 (9.8–36.4)	16.5 (10.1–36.4)	15.3 (9.8–29.1)
Sex (male/female), *n*	50/58	27/25	10/15
Tumor location, *n* (%)			
Intrasellar	1 (1)	0	0
Extrasellar	10 (9)	8 (15)	0
Intra- and extrasellar	40 (37)	28 (54)	12 (48)
n.a.	58 (53)	16 (31)	13 (52)
Tumor size, (cm^2), median (range)	8.0 (1.5–98.8)	12.0 (1.5–98.8)[a]	6.13 (1.5–9.0)[a]
Degree of resection, *n* (%)			
Total resection	44 (41)	21 (40)	13 (52)
Subtotal resection	54 (50)	29 (56)	10 (40)
n.a.	10 (9)	2 (4)	2 (8)
Hypothalamic involvement, *n* (%)			
Proven HI	52 (48)	52 (48)	
No HI	25 (23)		25 (23)
Not specified	31 (29)		
Radiotherapy, *n* (%)	36 (33)	20 (38)	7 (28)
n.a.	13 (14)	2 (1)	1 (0.25)
Repeated surgery, *n* (%)	23 (21), 39 n.a.	17 (33), 17 n.a.	3 (12), 5 n.a.
Overall survival, 20 years	0.98 ± 0.24	0.96 ± 0.04	1.0
Event-free survival, 20 years	0.63 ± 0.91	0.75 ± 0.08	0.63 ± 0.17
BMI-SDS at diagnosis, median (range)	+0.73 (−2.7–+7.0)	+0.9 (−2.6–+7.0)	−0.1 (−2.7–+4.3)
First symptom in history, *n* (%)			
Headache	43 (40)	23 (44)	10 (40)
Visual impairment	9 (8)	6 (12)	1 (4)
Neurological findings	9 (8)	7 (14)	1 (4)
Growth retardation	7 (7)	1 (2)	4 (16)
Diabetes insipidus	3 (3)	1 (2)	2 (8)
Other	3 (3)	2 (4)	–
n.a.	36 (33)	12 (23)	7 (28)
Duration of history months (range)	12 (0–108)	8 (0–96)	15 (0.1–96)

Abbreviations: BMI-SDS, body mass index standard deviation scores; HI, hypothalamic involvement; n.a., not available.
[a]*P* value <.01.

groups of participants (with and without HI). As shown in Figure 2, participants with HI developed a significant increase ($P = .000$) in BMI SDS during the first 8–12 years after diagnosis (median BMI change: +4.29 SD), whereas those without HI showed no significant increase in BMI SDS (median BMI change: +0.32 SD). Interestingly, analysis after more than 12 years of follow-up with a median interval of 16.9 years (range: 12–36.4 y) showed similar results: The median BMI in 22 participants without HI was +0.80 SD; the mean BMI in 45 participants with HI was +4.59 SD. Changes in BMI SDS between diagnosis and follow-up of more than12 years compared with the changes between diagnosis and 8–12 years of follow-up did not reach statistical significance. This indicates that the significant BMI increase and consequent development of hypothalamic obesity stabilized, plateauing after 8–12 years of follow-up in both groups.

Neuropsychological Status and Quality of Life

Neuropsychological status and QoL were evaluated using the EORTC QLQ-C30 questionnaire in 22 participants without HI and 50 participants with HI and by the MFI-20 questionnaire in 23 participants without HI and 48 participants with HI. When analyzing the functioning domains of the EORTC QLQ-C30 questionnaire, the only detectable difference was physical functioning (Fig. 3A). Participants without HI showed a better response ($P = .001$) in this domain (mean percentage: 97.6%) than participants with HI (mean percentage: 85.0%). When analyzing symptom scales of the EORTC QLQ-C30 questionnaire, participants with HI showed more pathological symptoms in 2 domains (dyspnea and diarrhea) than participants without HI (Fig. 3B): Complaints about dyspnea were more frequently detectable ($P = .033$) in participants with HI

Table 2. Psychosocial status of childhood-onset craniopharyngioma patients recruited in HIT Endo with and without HI

Attributes	Patients, *n* (%)	Patients with HI, *n* (%)	Patients without HI, *n* (%)	*P* value
Number of patients	89	42	22	
Married/partner	15 (17), 9 n.a.	**4 (10)**	**7 (32), 1 n.a.**	**.036**
Children/pregnant	2 (2), 10 n.a.	0 (0), 5 n.a.	2 (9), 2 n.a.	n.s
Friends	57 (46), 4 n.a.	28 (67)	20 (91)	n.s
Professional education	76 (85)	36 (86)	22 (100)	n.s
Employed	62 (70), 3 n.a.	28 (67)	19 (86)	n.s
Driver's license	53 (60), 2 n.a.	**21 (50)**	**19 (86)**	**.012**
Psychological treatment	38 (35)	13 (31)	9 (41)	n.s

HI, hypothalamic involvement; n.a., not available; n.s., not significant.

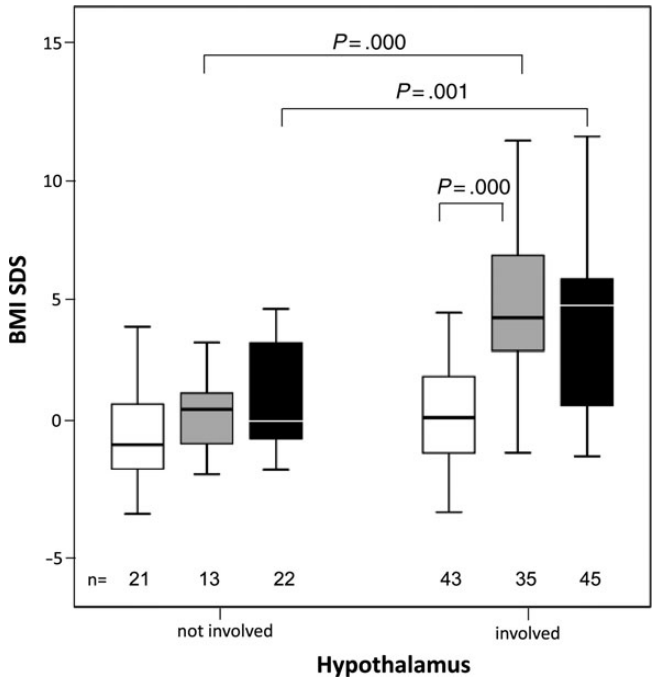

Fig. 2. Weight development in childhood-onset craniopharyngioma patients recruited in HIT Endo according to hypothalamic involvement. Body mass index (BMI) SDS is shown at time of diagnosis and at 2 intervals after diagnosis (8–12 years and more than 12 years). White boxes: BMI at diagnosis; grey: 8–12 year follow-up; black: more than 12 year follow-up. The horizontal line in the middle of the box depicts the median. The top and bottom edges of the box respectively mark the 25th and 75th percentiles. Whiskers indicate the range of values that fall within 1.5 box-lengths.

(14.7%) than in participants without HI (3.0%), as were complaints regarding diarrhea, which was present in 12.7% with HI versus 1.5% in participants without HI.

In the MFI-20 questionnaire, participants with HI showed a higher score in the domains of physical fatigue (mean score of 9.7 vs 7.2) and reduced motivation (mean score of 7.8 vs 6.3) (Fig. 3C). The scores of the other MFI-20 domains (general fatigue, reduced activity, and mental fatigue) were comparable in CP participants with and without HI.

We also compared neuropsychological status and QoL in participants who received XRT and participants without XRT. EORTC QLQ-C30 questionnaires were analyzed in 59 participants without XRT and 34 participants with XRT, and MFI-20 questionnaires were analyzed in 60 participants without XRT and 32 participants with XRT. We did not observe any significant differences between irradiated and nonirradiated participants for any of the EORTC OLQ and MFI-20 domains (data not shown).

Psychosocial Status

To address previously unanalyzed long-term outcomes in CP participants, we measured psychosocial parameters such as married/partner, offspring, professional education, employment, and having a driver's license in the 89 childhood-onset CP participants who had reached adulthood (age >20y) (Table 2). In a second-round psychosocial status analysis, healthy, adult siblings of our adult CP participants served as controls (Table 3). In total, we were able to contact 48 siblings of 42 participants. Because only persons over 20 years of age could be included in this second-round analysis, we could analyze only 35 of the 42 adult participants with siblings and only 30 of their 48 healthy siblings. Differences were striking in the offspring parameter. In total, only 2 of the 89 CP participants (2%) surviving to adulthood reported having offspring, and neither participant had HI. In the second-round analysis of 35 adult CP participants with 30 healthy, adult siblings, 11 (37%) of the 30 adult healthy siblings reported having offspring. Significant differences were also detectable in the parameter of having a driver's license: only 60% of adult CP participants reported having a driver's license vs 97% of the healthy adult siblings. In participants with HI, the percentage of participants with a driver's license was much lower (47%). Differences in terms of the married/partner parameter were also detectable between participants with and without HI. Only 10% of participants with HI reported being married or in a live-in partnership, whereas 32% of participants without HI were either married or in a live-in partnership. No differences could be detected for the parameters "having friends," "being employed," or "professional education".

Discussion

CPs, although benign, are associated with significant mortality and have reported overall mortality rates 3 to 5 times higher

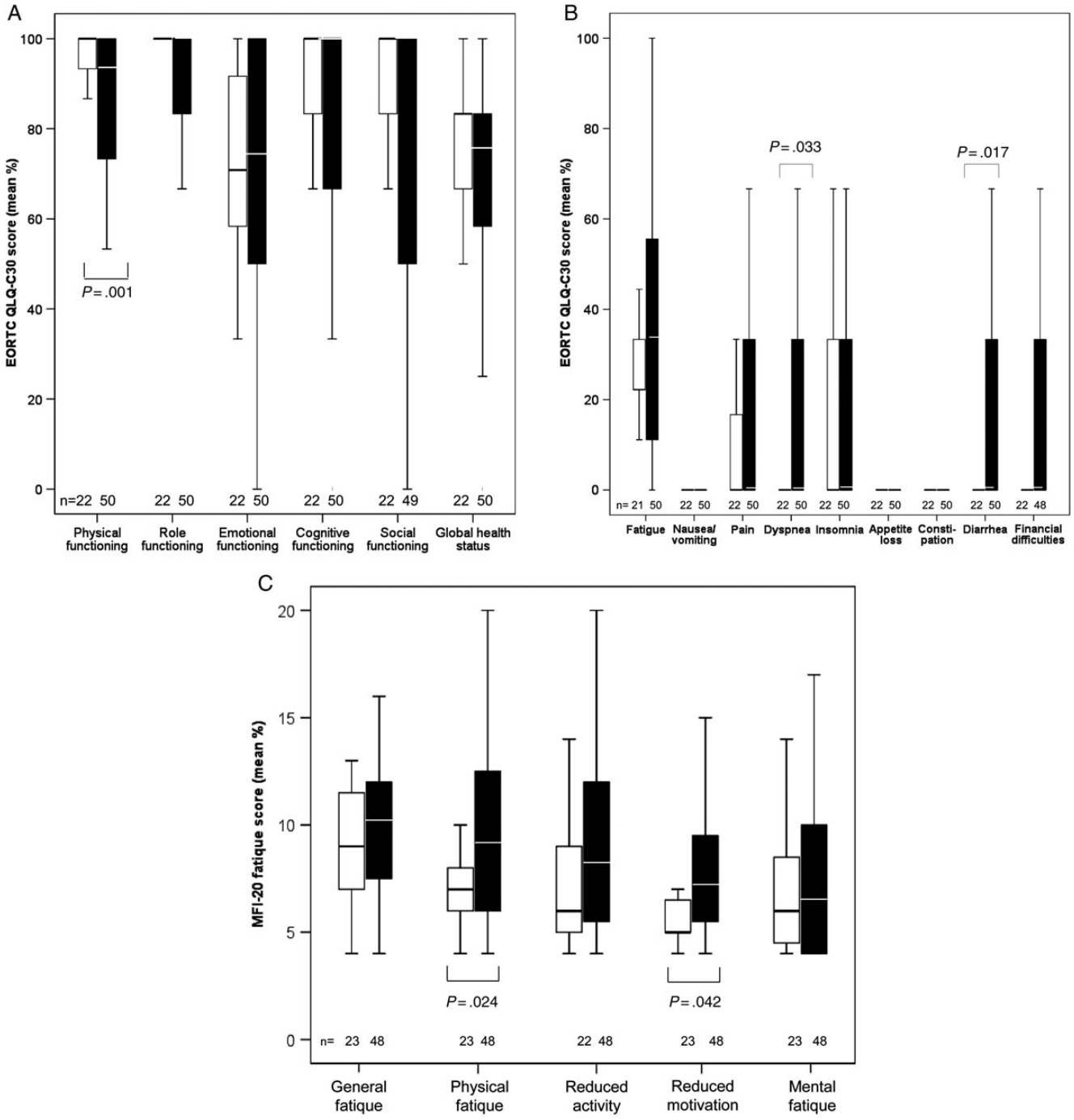

Fig. 3. EORTC QLQ-C30 functioning domains (A) and symptom scales (B) and MFI-20 fatigue domains (C) in childhood-onset craniopharyngioma patients (recruited in HIT Endo) according to hypothalamic involvement. White boxes: patients without hypothalamic involvement. Black boxes: patients with hypothalamic involvement. The horizontal line in the middle of the box depicts the median. The top and bottom edges of the box respectively mark the 25th and 75th percentiles. Whiskers indicate the range of values that fall within 1.5 box-lengths.

than those of the general population.[11,12] The OS rates (which reflect the effect of multiple treatments) described in children-only series range from 83% to 96% at 5 years[7,13–17] and 65%–100% at 10 years,[14–16,18–23] averaging 62% at 20 years.[24] However, unlike these previous long-term follow-up analyses, our study includes the largest cohort of childhood-onset CP reported to date, together with psychosocial parameters that have not been analyzed before. Our results show an OS of 88% of all CP participants. However, we report a significantly lower OS rate in participants with HI (84% versus 95% in participants without HI) ($P = .006$) and lower scores in psychosocial parameters (eg, living in a married/partner

Table 3. Psychosocial status of adult childhood-onset craniopharyngioma patients recruited in HIT Endo and controls (siblings >20 years of age at evaluation)

Attributes	Adult Patients, *n* (%)	Adult Siblings, *n* (%)	Adult Patients with HI, *n* (%)	Adult Siblings of Adult Patients with HI, *n* (%)	Adult Patients without HI, *n* (%)	Adult Siblings of Adult Patients without HI, *n* (%)
Number of patients	35	30	17	11	10	8
Married/partner	7 (20%)	12 (40%)	2 (12%)	3 (27%)	3 (30%)	4 (50%)
Children/pregnancy	**1 (3%)[a]**	**11 (37%)[a]**	0 (0%)	3 (27%)	1 (10%)	5 (63%)
Friends	23 (66%)	24 (80%)	10 (59%)	8 (73%)	10 (100%)	6 (75%)
Professional education	30 (86%)	28 (97%)	14 (82%)	11 (100%)	10 (100%)	8 (100%)
Employed	24 (69%)	20 (67%)	11 (65%)	6 (54%)	8 (80%)	7 (88%)
Driver's license	21 (60%)[a]	29 (97%)[a]	8 (47%)[a]	10 (91%)[a]	9 (90%)	8 (100%)
Psychological treatment	12 (34%)[a]	1 (2%)[a]	6 (35%)	0 (0%)	3 (30%)	0 (0%)

HI, hypothalamic involvement; n.a., not available.
[a]*P* value <.05.

relationship, having offspring, and holding a driver's license), severe QoL-compromising outcomes (eg, diminished physical functioning and motivation and physical fatigue) and other pathological sequelae (eg, obesity, dyspnea, and diarrhea). That said, PFS does not appear to be related to HI, nor does the degree of surgical resection seem to have a significant impact on OS and PFS rates. The severity and breadth of the above outcomes demonstrate the clinical relevance of HI at diagnosis with the development of hypothalamic syndrome and consequent long-term outcomes in CP survivors.

The above-mentioned significant differences in long-term survivors of CP with HI regarding offspring can be explained by the frequent pituitary hormone dysregulation resulting in central hypogonadism and infertility.[25] Furthermore, differences regarding having a driver's license are likely, at least in part, indications of compromised visual abilities. Analyses by Dekkers et al[26] showed general fatigue and physical fatigue to be increased in CP patients compared with healthy controls, which were explained by the high prevalence of metabolic and visual morbidity in CP patients. The scoring of the other fatigue domains, especially mental fatigue, was comparable in patients with and without HI. The current study confirms these findings based on our analysis of the MFI-20 questionnaire, which showed higher physical fatigue and reduced motivation in the participants with HI (those who suffer from obesity and visual morbidity).

It is not clear whether age at diagnosis represents a prognostic factor for survival. Some studies have shown that the youngest patients have better survival rates;[11] others have found better outcome in older patients.[27,28] Our data did not show any significant differences in OS with respect to age at diagnosis. The role of sex as a prognostic factor has not been definitively established; some authors report a higher mortality among females,[11,12] but others have not found any differences between the sexes.[16,29,30] We also did not find any differences between the sexes.

Several studies[27,30–32] report that age at tumor diagnosis does not seem to affect the risk of recurrence However, this conclusion is frequently based on analyses of heterogeneous single-center cohorts comprising both childhood- and adult-onset CP patients. Reports based on more age-homogeneous cohorts have shown that age at presentation may indeed affect the risk of recurrence.[28,31] In a series of 75 children, De Vile et al[18] found that age less than 5 years was a significant predictive factor for recurrence. Our study supports these findings, showing lower progression-free survival rates in participants younger than 5 years at diagnosis.

Regarding other prognostic factors possibly impacting relapse and/or morbidity, Weiner et al[31] did not observe an effect of tumor size on relapse rates, which we did not detect either. Nevertheless, we observed a significantly larger tumor size in our subgroup of participants with HI compared with the group without HI, indicating an indirect association between tumor size and higher morbidity. Also, the development of diabetes insipidus seems not to be a clinical marker for OS or PFS since (at least in our cohort of those with and without HI) no differences could be detected between patients who needed DDAVP substitution and those who did not.

Regarding effects of date of diagnosis, the lower survival rates reported earlier[13–16] usually reflected data from earlier series that occurred before modern advances in microsurgery, neuroimaging, and radiotherapy. However, we could not detect any significant differences in OS for CP patients treated before and after 1990.

One of the most striking and, confounding complications in childhood-onset CP is hypothalamic obesity, which occurs in 40%–66% of CP patients.[33,34] What is clear is that major risk factors for the development of hypothalamic obesity or other manifestations of hypothalamic syndrome are HI and/or treatment-related lesions.[7,20,35,36] Long-term survivors with HI in particular suffer from severe obesity and impaired QoL.[3,37] Our results confirm the association between HI and severe obesity: participants with HI developed a significantly higher increase in BMI SDS compared with those without HI within a follow-up time of 8–12 years. The association between HI and obesity has also been reported in previous studies,[7,35,38] and weight gain has been shown to occur mainly in the first year of follow-up.[23,39] Previous follow-up studies stated the prevalence of hypothalamic obesity but were not positioned to analyze weight development in detail during long-term

follow-up.[12,16,29] In the present study, we were able to analyze BMI development after a follow-up interval of more than 12 years. We demonstrated that no further significant increase in BMI SDS could be detected after 12 years of follow-up. Accordingly, this study is the first to report on a stabilization of hypothalamic obesity during long-term follow-up in childhood-onset CP patients. However, even after stabilization, the median BMI in participants with hypothalamic obesity after more than 12 years of follow-up was significant at +5.0 BMI SDS. It remains speculative whether this BMI represents the maximal amount of weight a body can obtain, albeit under pathological conditions. We contend that prevention of weight increase by using the least invasive surgical extraction strategies possible for CP patients with HI seems to be the best strategy for the problem of hypothalamic obesity; the treatment of hypothalamic obesity is complicated because therapeutic options are not yet available for this clinical syndrome.

Obesity is well known to be one of the main risk factors for chronic diseases and related disabilities. Obesity—regardless of origin—results in an increased risk of metabolic syndrome and cardiovascular disease.[38,40] The previously mentioned CP with HI outcomes of diminished physical functioning, as well as dyspnea, are conceivable comorbidities described in metabolic syndrome. In addition, obstructive sleep apnea syndrome is prevalent in obese CP patients and contributes to dyspnea symptoms.[41,42] Diarrhea also appears to be a major complaint of long-term survivors of CP, although (to our knowledge) the current study is the first to report this symptom in terms of long-term sequelae of CP with HI. Since diarrhea is a symptom of elevated intestinal motility, this finding might be a result of increased vagal activity, which is known in CP patients.[35] In addition, several reports exist of irritable bowel syndrome being linked to pathologies of the hypothalamic pituitary adrenal axis.[43] The interactions of diverse pharmacological drugs such as thyroxin, sexual steroids, and methylphenidate or psychotropic drugs—all or some of which have to be taken by many CP patients—are likely explanations for the above-mentioned occurrence of elevated intestinal motility in long-term survivors of CP.

The results of our study are limited due to its retrospective analysis and, as indicated, some observations are speculative at this point. A specific grading of HI, as performed in recent prospective studies,[3,4,44] would have been helpful but was not possible due to the quality of neuroradiological imaging in our retrospective analysis. We chose to calculate BMI SDS according to the standards of Rolland-Cachera[8] because these standards allow calculation of individual BMI SDS for a wide age range from early childhood to adulthood.

Based on our longitudinal analysis of this—thus far—largest published cohort of long-term survivors of childhood CP, we conclude that not only OS but also neuropsychological and psychosocial status are significantly impaired in long-term survivors of CP with HI. These findings are in line with a recent study by Fjalldal et al[45] on long-term survivors of childhood CP in which HI was found to be associated with lower cognitive performance and psychosocial health. The most pervasive, as well as the most unmanageable, of these outcomes is the weight gain that leads to severe hypothalamic obesity in CP patients with HI and reaches a certain plateau after 12 years of follow-up. Since surgical radicality has no impact on relapse and progression rates, gross-total resection should be avoided in cases of HI to prevent further hypothalamic damage. Further research on treatment options for hypothalamic sequelae, especially the seemingly unmanageable early-life weight gain progression to obesity, is warranted.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology* (http://neuro-oncology.oxfordjournals.org/).

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