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Safety of Growth Hormone Replacement Therapy in Childhood-Onset Craniopharyngioma: A Systematic Review and Cohort Study

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Keywords
Growth hormone replacement therapy · Childhood-onset craniopharyngioma · Treatment safety · Tumor progression · Secondary neoplasms

Abstract
Introduction: Survival of childhood-onset craniopharyngioma (cCP) is excellent; however, many survivors suffer from hypothalamic-pituitary dysfunction. Growth hormone replacement therapy (GHRT) is of high importance for linear growth and metabolic outcome. Optimal timing for initiation of GHRT in cCP is on debate because of concerns regarding tumor progression or recurrence. ***Methods:*** A systematic review and cohort studys were performed for the effect and timing of GHRT on overall mortality, tumor progression/recurrence, and secondary tumors in cCP. Within the cohort, cCP receiving GHRT ≤1 year after diagnosis were compared to those receiving GHRT >1 year after diagnosis. ***Results:*** Evidence of 18 included studies, reporting on 6,603 cCP with GHRT, suggests that GHRT does not increase the risk for overall mortality, progression, or recurrent disease. One study evaluated timing of GHRT and progression/recurrence-free survival and found no increased risk with earlier initiation. One study reported a higher than expected prevalence of secondary intracranial tumors compared to a healthy population, possibly confounded by radiotherapy. In our cohort, 75 of 87 cCP (86.2%) received GHRT for median of 4.9 years [0.0–17.1]. No effect of timing of GHRT was found on mortality, progression/recurrence-free survival, or secondary tumors. ***Conclusion:*** Although the quality of the evidence is low, the available evidence suggests no effect of GHRT or its timing on mortality, tumor progression/recurrence, or secondary neoplasms in cCP. These results support early initiation of GHRT in cCP aiming to optimize linear growth and metabolic outcome. Prospective studies are needed to increase the level of evidence upon the optimal timing to start GHRT in cCP patients.

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Introduction

Survival of childhood-onset craniopharyngioma (cCP) is excellent; however, quality of life is often deprived because of hypothalamic-pituitary damage [1]. As severity of hypothalamic damage has been related to the extent of neurosurgery, it has been advocated to shift the neuro-surgical approach from gross-total resection (GTR) to limited resection (LR) [2, 3]. A drawback of LR and accepting tumor rest is, however, an increased risk for growth of tumor rest, necessitating second surgery and/or radiotherapy [4].

Of all pituitary deficiencies, growth hormone deficiency (GHD) is most common in cCP and is observed in 26–75% at diagnosis and in 70–92% after tumor treatment [4, 5]. GHD has a significant negative effect on longitudinal growth [6]. In addition, GHD has negative effects on lipid and glucose homeostasis, lean and fat mass, as well as on bone mineral density and possibly even on cognitive outcome of the young child [7–11]. To prevent such consequences of GHD, timely replacement of GHD is of great importance.

Craniopharyngioma cells have been shown to express high levels of insulin-like growth factor-1 and growth hormone (GH) receptors, and therefore it has been questioned whether GH replacement therapy (GHRT) influences cCP recurrence or regrowth [5]. A recent consensus statement of the Growth Research Society concluded that: "although GH and insulin-like growth factor-1 have been shown in vitro to have a "permissive role" for carcinogenesis, there are no clinical studies that show that GHRT in patients surviving a brain tumor, after achieving complete remission, leads to increased recurrence rates" [12]. Data on cancer survivors are limited, but more solid data were produced in low-grade tumors, such as in adult benign pituitary adenomas, in which no association was found between GHRT and tumor recurrence [13, 14]. With these results in mind, GHRT is considered safe in low-grade tumors, such as cCP.

The effect of timing of the start of GHRT is however still an issue of debate; the Lawson Wilkins Pediatric Endocrinology Society Drug and Therapeutics Committee recommends to start GHRT 1 year after completion of tumor therapy, but the Growth Hormone Research Society (GRS) recommends that this interval may be as short as 3 months in children with radiologically proven stable residue of craniopharyngioma who have significant growth failure and metabolic disturbance [15]. Despite this recommendation, the optimal timing of the start of GHRT is often debated within the multidisciplinary teams, outweighing the potential benefits against the harms of GHRT. Especially for children with proven GHD and CP, to wait a year to commence with GHRT may significantly reduce height potential and have negative metabolic effects. To determine the optimal timing of the start of GHRT, there is a need for more studies evaluating the safety of GHRT and its timing. For this reason, we performed a cohort studys evaluating the effect of GHRT and its timing on mortality, progression/recurrence of cCP, and/or secondary neoplasms. In parallel, we conducted a systematic review to provide a comprehensive overview of the current state of the art on the safety of GHRT and its timing.

Methods

Systematic Review

The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) checklist was used to structure the systematic review [16]. A literature search was conducted using two electronic databases (MEDLINE and Embase) (from January 1, 1980 up to December 31, 2021). We developed a search strategy in collaboration with a trained clinical librarian using Medical Subject Headings/Emtree terms and text words related to GHRT and cCP. Details of the search strategy are shown in online supplementary table 1 (for all online suppl. material, see https://doi.org/10.1159/000531226). The reference lists from relevant reviews and included studies were screened for additional studies that were not identified by our initial search strategy. We used the following predefined selection criteria: (1) study population of at least 20 patients diagnosed with cCP (at age <18 years), (2) patients who received GHRT for GHD, (3) at least one outcome (mortality, tumor progression/tumor recurrence, or secondary neoplasm), as defined by the authors, on safety of GH was reported, and (4) published in the English language. Only studies with original data were considered (e.g., RCTs or cohort studies). When multiple articles with (partially) overlapping study populations were identified, the article with the most recent publication date or with the longest follow-up time was included. When the amount of overlap was unclear, we included both studies reporting the possibility of overlap. The following data were extracted: study population, comparison group, follow-up duration, type of cCP treatment, information on GHRT, and relevant outcomes (mortality, tumor progression/tumor recurrence, or secondary neoplasms). All effect measures reported of the outcome were included (e.g., number of events, prevalence, risk ratio, progression-free survival [PFS]). Risk of bias assessment was based on previously described checklists according to evidence-based medicine criteria (online suppl. Table 2) [17, 18]. Two reviewers (J.v.S. and E.K.) evaluated studies independently using Rayann (i.e., study selection (both title/abstract and full text phase), data extraction, and risk of bias assessment), and disagreements were resolved by consensus.

Cohort Study

Patients

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was used to structure our cohort studys [19]. A retrospective single-center cohort studys

was conducted. With the use of PALGA (Pathologisch Anatomisch Landelijk Geautomatiseerd Archief), the Dutch cohort of children (≤18 years) diagnosed with cCP during the period 2004–2021 was retrieved [20]. All patients known at the Princess Máxima Center for pediatric oncology, who had been diagnosed with a cCP from 2004 to 2021 (either proven histologically or clinically very likely based on imaging results) and had a minimal follow-up of 1 year were included. Informed consent was obtained from the legal guardian and/or patient (if age 12 and up) for the use of data.

Data Collection

Data on sex at birth, age, tumor and treatment-related variables, and endocrine outcomes were collected. Data on GHRT were collected, including type of GHRT, time between diagnosis and start of GHRT, and duration of GHRT. For timing of GHRT, GHRT was divided into two subgroups: GHRT started within 1 year after cCP diagnosis and GHRT started later than 1 year after cCP diagnosis.

Treatment

Type of resection was based on the report of the neurosurgeon in combination with the report of the radiologist, or, if not available, based on the documentation of the treating oncologist. The upfront surgical procedure (within the first 3 months after cCP diagnosis) was classified into cyst drainage/fenestration (eCD/F), LR, near total resection (NTR), and GTR. An endoscopic cyst drainage or fenestration without further resection of tumor tissue reported by the neurosurgeon and/or radiologist, was scored as eCD/F. LR was defined as less than 95% of the tumor resected or a partial resection (with obvious residual tumor mass present) reported by the neurosurgeon and/or radiologist. NTR was defined as more than 95% of the tumor resected, but not all tumor tissue removed. If exact percentages were not reported, NTR was based on neurosurgical and/or radiologist reporting: NTR or reports stating that almost all tumor was removed and little, minimal, or minor tumor tissue had been left (residual small enhancement lesion but no apparent tumor mass). GTR was defined as having removed all tumor tissue, stated both by the neurosurgeon and radiologist. If more than one surgical procedure was performed within the first 3 months, the most invasive type of resection was classified.

Tumor Progression/Recurrence

Tumor progression was defined as growth of residual tumor volume (cystic and/or solid) after any cCP treatment (excluding GTR) on magnetic resonance imaging scans as reported by a neuroradiologist for which an intervention was needed. Recurrence of tumor was defined as newly identified cCP after a GTR on imaging scans, as reported by a neuroradiologist for which an intervention was needed.

Statistical Analysis

Data are presented as mean ± SD or median [range] for continuous data, depending on the distribution. Data are presented as percentages for categorical variables. Between-group differences were evaluated by Student's t test for continuous data with a normal distribution, Mann-Whitney U test for continuous data with a skewed distribution, and by χ^2 test or Fisher's exact test for categorical data. To assess violation of normality distribution, QQ plot of the residuals and the Shapiro-Wilk's test were employed. Between group differences were evaluated by one-way analysis of variance for continuous data with a normal distribution, Kruskal-Wallis test for continuous data with a skewed distribution (skew variables were not further transformed), and by χ^2 test or Fisher's exact test for categorical data. To study the effect of possible risk factors on the outcome, univariate and multivariable Cox regression proportional hazard models were estimated. Independent variables to be included in the multivariable model were selected by estimating the univariate model and by considering the clinical relevance of each variable. The Cox regression model with initiation of GHRT as a time-dependent covariate was used to generate estimates of relative risk for tumor progression/recurrence in children with cCP. To estimate time to tumor progression/recurrence, Kaplan-Meier was used. Landmark analysis was used to study the impact of starting GHRT at different times after diagnosis on PFS. A p value of <0.05 was considered statistically significant. Analyses were performed by using SPSS version 27.0.

Results

Systematic Review

In total 278 articles were retrieved through the conducted MEDLINE and Embase search and three articles through other resources (Fig. 1). Of the 281 articles, 36 (possibly) met the inclusion criteria based on the abstract. After full-text screening, 18 articles were excluded because of a lack of a separate analysis for cCP patients, assessment of adult CP, less than 20 included cCP patients, or different outcome used. In total 18 studies were included [21–38].

Study Characteristics

All included studies were retrospective (n = 4) or prospective (n = 14) cohort studies. Four studies contained a control group with cCP patients not receiving GHRT. In total 6,603 cCP patients with GHRT were included (the number in each study varied between 22 and 1,038) and 108 cCP patients without GHRT. If reported, mean and median follow-up time from cCP diagnosis ranged between 3.2 and 15.9 years. Treatment consisted of surgery only or radiotherapy only or a combination of both, in the nine studies reporting on treatment modalities. Mean or median time between cCP diagnosis and start of GHRT ranged between 0.4 and 3.0 years. Due to missing data and clinical heterogeneity, pooling of data was not possible, and therefore, we provide descriptive results. For detailed information see Tables 1–3.

Mortality

Mortality of cCP patients was evaluated in total in six studies, including 2,438 cCP with GHRT [21, 22, 32, 36–38]. Prevalence of mortality of cCP was reported in

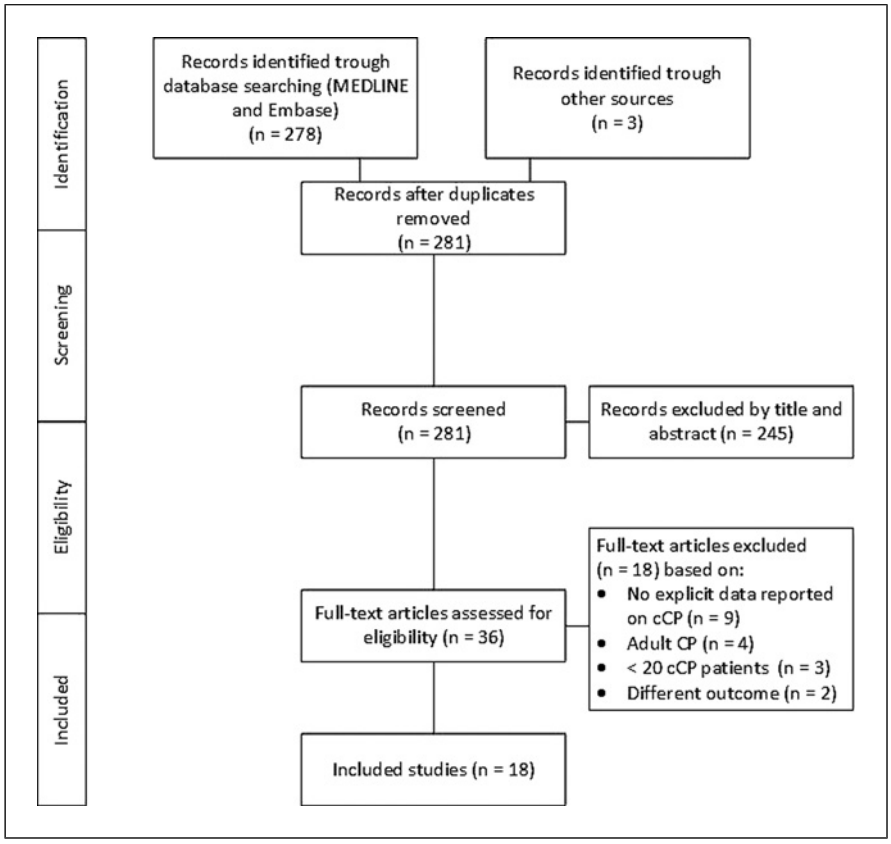

Fig. 1. Flowchart of the included studies.

five of the six studies and ranged between 0.2% and 6.4% in patients with cCP and GHRT. One study included cCP patients with and without GH, however, no report on the significance level of the difference between both groups was given. Two studies reported a significantly increased mortality risk in the patients with cCP and GHRT (both univariate analyses), compared to healthy controls. Reported mortality causes were death due to the craniopharyngioma itself, adrenal crisis, trauma, and infected ventricular-peritoneal shunt. Detailed information is reported in Table 1. No study reported on mortality in relation to the timing of GHRT.

Tumor Progression and Tumor Recurrence

Sixteen studies, including 6,405 cCP patients with GHRT, reported on tumor progression and/or recurrence in relation to GHRT [21–28, 30–35, 38]. In none of the studies the definition for the outcome "tumor progression" or "tumor recurrence" was provided. Four studies included a control group consisting of cCP patients without GHRT. Tumor progression/recurrence rate ranged between 4.2% and 50.0% in cCP patients with GHRT, compared to 39.4–57.1% in cCP without GHRT (reported in two studies). Two of the four studies including a control group reported the significance level of the difference between the cCP with and without GHRT and both reported no significant difference on tumor progression/recurrence rate (one study performed univariate analysis, one study performed a multivariate analysis, adjusted for degree of resection, radiotherapy, gender, age at diagnosis). One study reported on timing of GHRT and progression/recurrence-free survival and found no statistically significant difference between starting GHRT 1 year after cCP diagnosis versus 1–3 years, 3–5 years, and >5 years [26]. Detailed information is reported in Table 2.

Secondary Neoplasms

Two studies were found to report on secondary neoplasms after GHRT in cCP, including 1,738 cCP with GHRT [21, 38]. In the study of Bell et al. [16], 3 out of 994 cCP patients with GH (0.3%) developed a secondary neoplasm. No control group was included. In the study of Yuen et al. [38], who reported on a standardized incidence ratio (univariate) comparing cCP with GHRT to a healthy population, 2 of 744 cCP (0.27%) developed a new intracranial tumor and 4 of 744 cCP (0.54%) a new extracranial tumor. When compared to the general population, the risk

Table 1. Studies reporting on overall mortality in cCP with GHRT

First author, year of publication, study design	No. of participants	Follow-up from cCP diagnosis (mean or median) in years	cCP treatment	GHRT	Events	Effect size	Risk of bias
Stochholm et al. [36] (2012), prospective cohort	*n* = 41 cCP with GHRT Control group *n* = 40,468 healthy controls matched for age and gender	Not reported (whole cohort including other cancer diagnoses: maximum 48 years)	Not reported	Not reported	Not reported	Mortality risk for cCP with GHRT compared to healthy controls (univariate HR) Males = 16.9 (6.5–43.9)*, Females = 15.0 (3.4–67.2)*	SB: unclear risk; reason: the original cohort of eligible cCP patients is unknown AB: low risk; reason: outcome assessed in all patients (100%) of study cohort DB: low risk; reason: as blinding is not relevant for the outcome overall mortality, we judged this outcome at low risk of detection bias CF: high risk, no prognostic factors (e.g., diversity in treatment) taken into account
Yuen et al. [38] (2018), retrospective cohort	*n* = 744 cCP with GHRT Control group Age- and gender-specific incidence rates in the general population	Mean 6.4 years±4.8	Surgery only: *n* = 487 (65.5%) Surgery and radiotherapy: *n* = 170 (22.9%) Radiotherapy only: *n* = 33 (4.4%) Radiotherapy dose: not reported Unknown: *n* = 54 (7.2%)	GHRT timing after cCP diagnosis Mean 0.7 years (mean age at cCP diagnosis: 11.1±4.5/mean age at start GHRT 11.8±4.2) GHRT dose Mean 0.6 mg/d±0.4 GHRT duration Mean 6.1 years (mean age at start GHRT 11.8±4.2/mean age at stop GHRT 17.9±2.9)	Mortality: *n* = 22 observed (3.0%)/*n* = 7.86 (1.1%) expected	Mortality risk for cCP with GHRT compared to the general population (univariate SMR): 2.87 (1.79–4.34), *p* = 0.001*	SB: unclear risk; reason: the original cohort of eligible cCP patients is unknown AB: low risk; reason: in this study mortality was seen as an AE and it was mandatory to report them. As a result, although the exact number of participants with an outcome assessment was not reported, we assume that it was available for more than 75% of participants DB: low risk; reason: as blinding is not relevant for the outcome overall mortality, we judged this outcome at low risk of detection bias CF: high risk, no prognostic factors (e.g., diversity in treatment) taken into account
Taback et al. [37] (1996), prospective cohort	*n* = 157 cCP with GHRT Control group *n* = 751 idiopathic GHD with GHRT	Not reported	Not reported	Not reported	Mortality: cCP: *n* = 10 (6.4%) with GHRT versus Idiopathic GHD with GHRT: *n* = 10 (1.3%) Cause of death cCP Adrenal crisis (*n* = 3) Trauma (*n* = 2) cCP (*n* = 2) Infected shunt (*n* = 1) Aspiration (*n* = 1) Unknown (*n* = 1) Mortality risk for cCP with GHRT compared to idiopathic GHD with GHRT (univariate *p* value): *p* = 0.001*	Not reported	SB: unclear risk; reason: the original cohort of eligible cCP patients is unknown AB: low risk; reason: outcome assessed in all patients (100%) of study cohort DB: low risk; reason: as blinding is not relevant for the outcome overall mortality, we judged this outcome at low risk of detection bias CF: not applicable

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Table 1 (continued)

First author, year of publication, study design	No. of participants	Follow-up from cCP diagnosis (mean or median) in years	cCP treatment	GHRT	Events	Effect size	Risk of bias
Bell et al. [21] (2010), prospective cohort	*n* = 994 cCP with GHRT Control group No control group	Not reported	Not reported	Not reported	Mortality: *n* = 2 (0.2%) with GHRT Cause of death: cCP (*n* = 2)	Not reported	SB: unclear risk; reason: the original cohort of eligible cCP patients is unknown AB: low risk; reason: in this study mortality was seen as an AE and it was mandatory to report them. As a result, although the exact number of participants with an outcome assessment was not reported, we assume that it was available for more than 75% of participants DB: low risk; reason: as blinding is not relevant for the outcome overall mortality, we judged this outcome at low risk of detection bias CF: not applicable
Boekhoff et al. [22] (2018), prospective cohort	*n* = 71 cCP with GHRT of which *n* = 34 (47.9%) contGH *n* = 26 (36.6%) pedGH *n* = 11 (15.5%) adultGH Control group: *n* = 8 cCP without GHRT	ContGH: Median 16.6 years [9.9–27.2] PedGH: Median 13.5 years [9.8–33.8] AdultGH: Median 16.2 years [10.3–27.4] Control group 15.8 years [13.9–25.2]	ContGH Complete resection: *n* = 15 (44%) Incomplete resection: *n* = 17 (50.0%) Unknown: *n* = 2 (6%) PedGH: Complete resection: *n* = 8 (31%) Incomplete resection: *n* = 16 (61%) Unknown: *n* = 2 (8%) AdultGH: Complete resection: *n* = 3 (27%) Incomplete resection: *n* = 6 (54%) Unknown: *n* = 2 (18%)	GHRT timing after cCP diagnosis ContGH: mean 2.9 years (mean age at cCP diagnosis: 8.1/ mean age at GHRT initiation: 11) PedGH: mean 2.9 years (mean age at diagnosis: 8.1/mean age at initiation: 11) AdultGH: mean 9.1 years (mean age at diagnosis: 11.9/mean age at initiation: 21) GHRT dose Not reported GHRT duration ContGH: median 17 years [10–32] PedGH: median 6 years [1–17] AdultGH: median 6 years [0–16]	Mortality Overall: *n* = 1 (1.4%) ContGH: *n* = 1 (2.9%) PedGH: *n* = zero (0.0%) AdultGH: *n* = zero (0.0%) No GHRT: *n* = 1 (12.5%) OS rates: 100% (but elsewhere in this article the 2 fatal events as mentioned above where reported) Cause of death Not reported	Not reported	SB: high risk; reason: only 79 (28.2%) patients of total cohort were included AB: low risk; reason: outcome assessed in all patients (100%) of study cohort DB: low risk; reason: as blinding is not relevant for the outcome overall mortality, we judged this outcome at low risk of detection bias CF: not applicable

Table 1 (continued)

First author, year of publication, study design	No. of participants	Follow-up from cCP diagnosis (mean or median) in years	cCP treatment	GHRT	Events	Effect size	Risk of bias
			Control group Complete resection: *n* = 4 (50%) Incomplete resection: *n* = 4 (50%) Radiotherapy ContGH: 9 (26%) PedGH: 15 (54%) AdultGH: 3 (27%) Control group: 1 (12%) Mean dose of all groups: 54 Gy				
Rose et al. [32] (2020), prospective cohort	*n* = 431 cCP with GHRT Control group No control group	Not reported	Cranial radiotherapy: *n* = 137 (32%) Radiotherapy dose: not reported No radiotherapy: *n* = 268 (62%) Unknown: *n* = 26 (6%)	GHRT timing after cCP diagnosis Not reported Median age at cCP diagnosis: with RT: 7.9 years/without RT: 7.3 years Median age at GHRT initiation: with RT: 8.3 years/without RT: 7.9 years GHRT dose: cCP with RT: median 0.17 mg/kg/w [0.10–0.25] cCP no RT: median 0.18 mg/kg/w [0.12–0.26] GHRT duration: cCP with RT median 8.1 [5.4–12.1] cCP no RT median 13.3 [11.3–15.7]	Mortality: *n* = 6 (1.4%) with GHRT Cause of death: cCP recurrence (*n* = 2) Intracranial hemorrhage (*n* = 1) Unknown (*n* = 3)	Not reported	SB: unclear risk; reason: the original cohort of eligible cCP patients is unknown AB: low risk; reason: in this study mortality was seen as an AE and it was mandatory to report them. As a result, although the exact number of participants with an outcome assessment was not reported, we assume that it was available for more than 75% of participants DB: low risk; reason: as blinding is not relevant for the outcome overall mortality, we judged this outcome at low risk of detection bias CF: not applicable

cCP, childhood-onset craniopharyngioma; GHRT, growth hormone replacement therapy; GHD, growth hormone deficiency; HR, hazard ratio, SMR, standardized morality ratio; SB, selection bias; AB, attrition bias; DB, detection bias; CF, confounding; PedGH, growth hormone treatment started at childhood; ContGH, continued growth hormone therapy in pediatric and adult life; AdultGH, growth hormone therapy started in adulthood; RT, radiotherapy; AE, adverse event. Numbers presented in mean ± SDS or median [range]. *statistically significant.

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Table 2. Studies reporting on tumor progression or recurrence in cCP with GHRT

First author, year of publication, study design	No. of participants	Follow-up from cCP diagnosis (mean or median) in years	cCP treatment	GHRT	Events	Effect size	Risk of bias
Darendeliler et al. [26] (2006) (KIGS), prospective cohort	*n* = 1,038 cCP with GHRT Control group No control group	cCP without recurrence: median 5.8 year [1.6–10.7] cCP with recurrence: 10.3 years [not reported]	Surgery: *n* = 513 (49.4%) Surgery and radiotherapy: *n* = 307 (29.6%) Surgery and radiotherapy and chemotherapy: *n* = 25 (2.4%) Radiotherapy dose Not reported Unknown: *n* = 193 (18.6%)	GHRT timing after cCP diagnosis With recurrence versus without recurrence 0.5 year versus 0.9 year Time intervals <1 year: *n* = 835 patients 1–3 years: *n* = 130 patients 3–5 years: *n* = 35 patients 5 years: *n* = 38 patients GHRT dose: not reported GHRT duration: not reported	Outcome definition Not reported cCP recurrence *n* = 121 (11.7%)	Univariate progression/ recurrence-free survival: GHRT start within 1 year after cCP diagnosis versus 1–3 years versus 3–5 years versus >5 years (log-rank 0.8386, *p* = 0.84)	SB: unclear risk; reason: the original cohort of eligible cCP patients is unknown AB: low risk; reason: outcome was assessed in 956/1,038 (92%) of the patients DB: unclear; reason: unknown if outcome assessors were blinded for important determinants CF: high risk; no prognostic factors (e.g., diversity in treatment) taken into account
Müller et al. [29] (2010), prospective cohort	*n* = 54 cCP with GHRT Control group: *n* = 60 cCP without GHRT	Total time: 3 years (no further information provided)	cCP with GHRT: Surgery: Complete resection: *n* = 25 (42%) Incomplete resection: *n* = 29 (58%) cCP without GHRT: Surgery: Complete resection: *n* = 23 (38%) Incomplete resection: *n* = 37 (62%) Radiotherapy (cCP with and without GHRT combined) Local external radiation: *n* = 30 (26%) Gamma knife: *n* = 2 (1.7%) Radiotherapy dose Not reported	GHRT timing after cCP diagnosis: Median 0.70 years [0.07–3.56] GHRT dose: not reported GHRT duration: not reported	Outcome definition: Not provided cCP recurrence: Not reported	Combination of recurrence, progression, and death: GHRT versus no GHRT or before initiation of GHRT (*p* value adjusted for degree of resection, radiotherapy, gender, age at dx): *p* = 0.911	SB: unclear risk; reason: the original cohort of eligible cCP patients is unknown AB: low risk; reason: outcome was assessed in 109/114 (95.6%) of the patients DB: unclear; reason: unknown if outcome assessors were blinded for important determinants CF: high risk; not all important factors (e.g., follow-up) taken into account
Boekhoff et al. [22] (2018), prospective cohort	*n* = *71* cCP with GHRT of which *n* = 34 (47.9%) contGH *n* = 26 (36.6%) pedGH *n* = 11 (15.5%)	ContGH: Median 16.6 years [9.9–27.2] PedGH: Median 13.5 years [9.8–33.8] AdultGH: Median 16.2 years [10.3–27.4]	ContGH: Complete resection: *n* = 15 (44%) Incomplete resection: *n* = 17 (50.0%) Unknown: *n* = 2 (6%) PedGH: Complete resection:	GHRT timing after cCP diagnosis ContGH: mean 2.9 years (mean age at cCP diagnosis: 8.1/mean age at GHRT initiation: 11) PedGH: mean	Outcome definition Not reported cCP recurrence Not reported	Progression/recurrence-free survival (mean %, univariate *p* value) PedGH: mean 0.321±0.144 ContGH: mean 0.693±0.108 AdultGH: 0.471 mean±0.205 No GHRT: 0.500±0.354, *p* = 0.0893	SB: high risk; reason: only 79 (28.2%) patients of total cohort were included AB: low risk; reason: outcome assessed in 65/79 (82.3%) of study cohort DB: unclear; reason: unknown if outcome assessors were

Table 2 (continued)

First author, year of publication, study design	No. of participants	Follow-up from cCP diagnosis (mean or median) in years	cCP treatment	GHRT	Events	Effect size	Risk of bias
	adultGH Control group: *n* = 8 cCP without GHRT	Control group 15.8 years [13.9–25.2]	*n* = 8 (31%) Incomplete resection: *n* = 16 (61%) Unknown: *n* = 2 (8%) AdultGH: Complete resection: *n* = 3 (27%) Incomplete resection: *n* = 6 (54%) Unknown: *n* = 2 (18%) Control group: Complete resection: *n* = 4 (50%) Incomplete resection: *n* = 4 (50%) Radiotherapy ContGH: 9 (26%) PedGH: 15 (54) AdultGH: 3 (27) Control group: 1 (12%) Mean dose of all groups: 54 Gy	2.9 years (mean age at diagnosis: 8.1/ mean age at initiation: 11) AdultGH: mean 9.1 years (mean age at diagnosis: 11.9/ mean age at initiation: 21) GHRT dose Not reported GHRT duration ContGH: median 17 years [10–32] PedGH: median 6 years [1–17] AdultGH: median 6 years [0–16]			blinded for important determinants CF: high risk; no prognostic factors (e.g., diversity in treatment) taken into account
Cowell et al. [25] (1995), prospective cohort	*n* = 62 cCP with GHRT Control group No control group	Not reported	Not reported	Not reported	Outcome definition Not reported cCP recurrence *n* = 7 (11.3%); 11 recurrences in these patients in total	Not reported	SB: low risk; reason: overall patient inclusion ranged between 71% and 100%, in 4/ 5 years >75% AB: low risk; reason: outcome assessed in all patients (100%) of study cohort DB: unclear; reason: unknown if outcome assessors were blinded for important determinants CF: not applicable
Moshang et al. [28] (1996) (NCGS), prospective cohort	*n* = 546 cCP with GHRT Control group No control group	Not reported Patient years at risk: Median 5.33 years [0.29–10.15]	Not reported	Not reported	Outcome definition Not reported cCP recurrence *n* = 35 (6.4%)	Not reported	SB: unclear risk; reason: the original cohort of eligible cCP patients is unknown AB: low risk; reason: outcome assessed in all patients (100%) of study cohort DB: unclear; reason: unknown if outcome assessors were blinded for important determinants CF: not applicable
Price et al. [30] (1998) (KIGS), prospective cohort	*n* = 488 cCP with GHRT Control group No control group	Not reported	Surgery: *n* = 251 (51.4%) Surgery and radiotherapy: *n* = 144 (29.5%) Radiotherapy: *n* = 12	GHRT timing after cCP diagnosis Median 1.56 years [0.56–12.48] Mean 2.23 years±1.88	Outcome definition Not reported cCP recurrence *n* = 54 patients (11%); in total 63 recurrences	Not reported	SB: unclear risk; reason: the original cohort of eligible cCP patients is unknown AB: low risk; reason: outcome assessed in all patients (100%) of study cohort

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Table 2 (continued)

First author, year of publication, study design	No. of participants	Follow-up from cCP diagnosis (mean or median) in years	cCP treatment	GHRT	Events	Effect size	Risk of bias
			(2.5%) Radiotherapy dose Not reported No treatment: *n* = 44 (9.0%) Unknown: *n* = 37 (7.6%)	GHRT dose: not reported GHRT duration: not reported	Incidence of recurrence: 0.045/ treatment year		DB: unclear; reason: unknown if outcome assessors were blinded for important determinants CF: not applicable
Clayton et al. [24] (1988), retrospective cohort	*n* = 23 cCP with GHRT Control group No control group	Mean 6.3 years [range 1.5–15.5]	Surgery: *n* = 23 (100%) Post-surgery radiotherapy: *n* = 10 (43%) Radiotherapy dose Not reported Later in follow-up radiotherapy: *n* = 6 (26.1%)	GHRT timing after cCP diagnosis Mean 2.5 years GHRT dose: not reported GHRT duration: not reported	Outcome definition Not reported cCP recurrence In total *n* = 8 patients (34.8%), of which: *n* = 5 patients (21.7%); 8 recurrences in total with GHRT versus *n* = 3 patients (13.0%); 4 recurrences in total before GHRT → No significant difference (data not reported) No recurrences in *n* = 10 patients with post-surgery radiotherapy, *n* = 13 cases did not receive post-surgery radiotherapy, *n* = 12 recurrences in *n* = 7 patients ($p < 0.01$)	Not reported	SB: unclear risk; reason: the original cohort of eligible cCP patients is unknown AB: low risk; reason: outcome assessed in all patients (100%) of study cohort DB: unclear; reason: unknown if outcome assessors were blinded for important determinants CF: not applicable
Maneatis et al. [27] (2000) (NCGS), prospective cohort	*n* = 785 cCP with GHRT Control group No control group	Not reported	Not reported	Not reported	Outcome definition Not reported cCP recurrence *n* = 50 (6.4%)	Not reported	SB: unclear risk; reason: the original cohort of eligible cCP patients is unknown AB: low risk; reason: outcome assessed in all patients (100%) of study cohort DB: unclear; reason: unknown if outcome assessors were blinded for important determinants CF: not applicable
Rohrer et al. [31] (2010), retrospective cohort	*n* = 22 cCP with GHRT Control group: *n* = 7 cCP without GHRT	Median 8.8 years [3.8–29]	Surgery (reported for cCP with and without cCP combined) Total removal *n* = 15 (51.7%) Subtotal removal: *n* = 14 (48.3%) Radiotherapy (reported for cCP with and without cCP combined): *n* = 10 (34.5%) Radiotherapy dose Not reported	Not reported	Outcome definition Not reported cCP recurrence *n* = 11 (50%) with GHRT versus *n* = 4 (57.1%) without GHRT	Not reported	SB: unclear risk; reason: the original cohort of eligible cCP patients is unknown AB: low risk; reason: outcome assessed in all patients (100%) of study cohort DB: unclear; reason: unknown if outcome assessors were blinded for important determinants CF: not applicable
Bell et al. [21] (2010) (NCGS),	*n* = 994 cCP with GHRT Control group	Not reported	Not reported	Not reported	Outcome definition Not reported	Not reported	SB: unclear risk; reason: the original cohort of eligible cCP patients is unknown

Table 2 (continued)

First author, year of publication, study design	No. of participants	Follow-up from cCP diagnosis (mean or median) in years	cCP treatment	GHRT	Events	Effect size	Risk of bias
prospective cohort	No control group				cCP recurrence *n* = 86 (8.7%)		AB: low risk; reason: in this study tumor progression/ recurrence was seen as an AE and it was mandatory to report them. As a result, although the exact number of participants with an outcome assessment was not reported, we assume that it was available for more than 75% of participants DB: unclear; reason: unknown if outcome assessors were blinded for important determinants CF: not applicable
Smith et al. [33] (2016) (NCGS), prospective cohort	*n* = 739 cCP with GHRT Control group No control group	Median 4.3 years [0.7–6.4]	Not reported	GHRT timing after cCP diagnosis At least 12 months GHRT dose: not reported GHRT duration: not reported	Outcome definition Not reported cCP recurrence *n* = 50 (6.8%) 30 (<9 years age at enrollment) = (0.025 recurrences/per year observation) 17 (9–13 years age at enrollment) = (0.017 recurrences/ per year observation) 3 (13+ years age at enrollment) = (0.005 recurrences/per year observation) (p = 0.0097)	Not reported	SB: unclear risk; reason: the original cohort of eligible cCP patients is unknown AB: low risk; reason: outcome assessed in all patients (100%) of study cohort DB: unclear; reason: unknown if outcome assessors were blinded for important determinants CF: not applicable
Yokoya et al. [34] (2017) (GeNeSIS), prospective cohort	*n* = 25 cCP with GHRT Control group: No control group	Not reported (for the whole cohort including other diagnoses: mean 3.2 years/median 2.7 years)	Not reported	Not reported	Outcome definition Not reported cCP recurrence *n* = 4 (16.0%)	Not reported	SB: unclear risk; reason: the original cohort of eligible cCP patients is unknown AB: unclear risk; reason: only reported for the whole cohort including other diagnoses, not specific for cCP reported DB: unclear; reason: unknown if outcome assessors were blinded for important determinants CF: not applicable
Yuen et al. [38] (2018), retrospective cohort	*n* = 744 cCP with GHRT Control group: No control group	Mean 6.4 years±4.8	Surgery only: *n* = 487 (65.5%) Surgery and radiotherapy: *n* = 170 (22.9%) Radiotherapy only: *n* = 33 (4.4%) Radiotherapy dose: not reported	GHRT timing after cCP diagnosis Mean 0.7 years (mean age at cCP diagnosis: 11.1±4.5/ mean age at start GHRT 11.8±4.2) GHRT dose: Mean 0.6 mg/d±0.4	Outcome definition: Not reported cCP recurrence: *n* = 31 (4.2%)	Not reported	SB: unclear risk; reason: the original cohort of eligible cCP patients is unknown AB: low risk; reason: In this study tumor progression/ recurrence was seen as an AE and it was mandatory to report them. As a result, although the exact number of participants

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Table 2 (continued)

First author, year of publication, study design	No. of participants	Follow-up from cCP diagnosis (mean or median) in years	cCP treatment	GHRT	Events	Effect size	Risk of bias
			Unknown: *n* = 54 (7.2%)	GHRT duration: Mean 6.1 years (mean age at start GHRT 11.8±4.2/ mean age at stop GHRT 17.9±2.9)			with an outcome assessment was not reported, we assume that it was available for more than 75% of participants DB: unclear risk; reason: unknown if outcome assessors were blinded for important determinants CF: not applicable
Child et al. [23] (2019) (GeNeSIS), prospective cohort	*n* = 271 cCP with GHRT Control group: No control group	Not reported (for the whole cohort including other diagnoses: mean 4.2 years±3.2)	Not reported	Not reported	Outcome definition: Not reported cCP recurrence: *n* = 37 patients (13.6%); 42 recurrences in total Crude Incidence (95% CI) (cases/ 1,000 patients years) CP recurrence: 26.32 (19.07–36.32)	Not reported	SB: unclear risk; reason: the original cohort of eligible cCP patients is unknown AB: low risk; reason: outcome assessed in all patients (100%) of study cohort DB: unclear; reason: unknown if outcome assessors were blinded for important determinants CF: not applicable
Rose et al. [32] (2020), prospective cohort	*n* = 431 cCP with GHRT Control group: No control group	Not reported	Cranial radiotherapy: *n* = 137 (32%) Radiotherapy dose: not reported No radiotherapy: *n* = 268 (62%) Unknown: *n* = 26 (6.0%)	GHRT timing after cCP diagnosis: Not reported Median age at cCP diagnosis: with RT: 7.9 years/without RT: 7.3 years Median age at GHRT initiation: with RT: 8.3 years/without RT: 7.9 years GHRT dose: cCP with RT: median 0.17 mg/kg/w [0.10–0.25] cCP no RT: median 0.18 mg/kg/w [0.12–0.26] GHRT duration: cCP with RT: median 8.1 [5.4–12.1] cCP no RT median 13.3 [11.3–15.7]	Outcome definition Not reported cCP recurrence: *n* = 20 (4.6%)	Not reported	SB: unclear risk; reason: the original cohort of eligible cCP patients is unknown AB: low risk; reason: In this study tumor progression/ recurrence was seen as an AE and it was mandatory to report them. As a result, although the exact number of participants with an outcome assessment was not reported, we assume that it was available for more than 75% of participants DB: unclear; reason: unknown if outcome assessors were blinded for important determinants CF: not applicable
Zucchini et al. [35] (2021), retrospective cohort	*n* = 112 cCP with GHRT Control group: *n* = 33 cCP without GHRT	Mean 7.6 years±4.3	Surgery (reported for cCP with and without GHRT combined): *n* = 145 (100%) Radiotherapy	GHRT timing after cCP diagnosis: Partial surgery versus radical surgery: mean 3.0	Outcome definition Not reported cCP recurrence: In total *n* = 67 patients (46.2% of 145) (*n* = 23 recurrences and *n* =	Not reported	SB: unclear risk; reason: the original cohort of eligible cCP patients is unknown AB: low risk; reason: outcome assessed in 139/145 (95.7%) of

Table 2 (continued)

First author, year of publication, study design	No. of participants	Follow-up from cCP diagnosis (mean or median) in years	cCP treatment	GHRT	Events	Effect size	Risk of bias
			(reported for cCP with and without GHRT combined): n = 56 (38%) Radiotherapy dose: Not reported	years±4.8 versus mean 1.3 years±0.6; p = 0.003* GHRT dose: not reported GHRT duration: not reported	44 regrowth of the residual lesion) In GHRT group In total n = 54 (48.2% of 112), of which Before GHRT: n = 27 (24.1% of 112) During GHRT n = 27 (24.1% of 112) In no GHRT group: n = 13 (39.4% of 33)		study cohort DB: unclear; reason: unknown if outcome assessors were blinded for important determinants CF: not applicable

cCP, childhood-onset craniopharyngioma; GHRT, growth hormone replacement therapy; SB, selection bias; AB, attrition bias; DB, detection bias; CF, confounding; KIGS, Pfizer International Growth Database; Dx, diagnosis; NCGS, National Cooperative Growth Study; GeNeSIS, Genetics and Neuroendocrinology of Short Stature International Study; PedGH, growth hormone treatment started at childhood; ContGH, continued growth hormone therapy in pediatric and adult life; AdultGH, growth hormone therapy started in adulthood; AE, adverse event. Numbers presented in mean ± SDS or median [range]. *statistically significant. Possible overlap of patients, data were all collected from the prospective cohort KIGS: Pfizer International Growth Database. Possible overlap of patients, data were all collected from the prospective cohort NCGS: National Cooperative Growth Study. Possible overlap of patients, data were all collected from the prospective cohort GeNeSIS: Genetics and Neuroendocrinology of Short Stature International Study.

for secondary intracranial tumors was increased with a standardized incidence ratio of 11.2 (1.26–40.50) (p = 0.035). In addition, they performed an univariate analysis for risk of secondary intracranial tumors, combining cCP and adult CP with GHRT, and found a trend toward an increased risk of radiotherapy (HR 3.47 [0.92–13.10], p = 0.067). For extracranial tumors no significant difference was identified. Detailed information is reported in Table 3. No study reported on secondary neoplasms in relation to timing of GHRT.

Risk of Bias Assessment according to Evidence-Based Medicine Criteria [14, 15]

Of the studies reporting on overall mortality, in one study there was a high risk of selection bias, because patient inclusion from the original cohort of eligible cCP was <75% (17%). In the other 5/6 studies, the risk of selection bias was unclear (83%). The risk of attrition bias (≥75% of the outcome was assessed in the study cohort) and detection bias (outcome assessors blinded for important determinants) was low in all studies reporting on mortality. Confounding bias was applicable in two studies, in both there was a high risk for confounding bias because no prognostic factors (e.g., diversity in treatment) were taken into account. In the studies reporting on tumor progression/recurrence, the risk of selection bias was unclear in 14/16 studies (88%), high in one study (6%), and low in another (6%). The risk of attrition bias was low in 15/16 studies (94%) and unclear in the other one (6%). Presence of detection bias was unclear in all studies. In all studies reporting on tumor progression/recurrence for which confounding bias was applicable, there was a high risk of confounding. In the studies reporting on the risk to develop a secondary neoplasm, selection bias and detection bias was unclear in both studies, while the risk of attrition bias was low. The risk of confounding, applicable to one study, was high. Detailed information on the reasoning for all risk of bias judgments is included in Tables 1–3.

Cohort Study

Patient Characteristics

In total, 166 children (aged <18 years) had been diagnosed with histology proven cCP in the Netherlands in the period 2004–2021, and were potentially eligible for inclusion in the study [26]. Of these, 105/166 (63%) were known in the Princess Máxima Center and could be asked informed consent for use of the data (examined and confirmed eligible). In total, 87/105 patients (83%) approved consent for use of data for this study and could thus be

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Table 3. Studies reporting on the risk of secondary neoplasm in cCP with GHRT

First author, year of publication, study design	No. of participants	Follow-up from cCP diagnosis (mean or median) in years	cCP treatment	GHRT	Events	Effect size	Risk of bias
Yuen et al. [38] (2018), retrospective cohort	n = 744 cCP with GHRT Control group Age- and gender-specific incidence rates in the general population	Mean 6.4 years±4.8	Surgery only: n = 487 (65.5%) Surgery and radiotherapy: n = 170 (22.9%) Radiotherapy only: n = 33 (4.4%) Radiotherapy dose: not reported Unknown: n = 54 (7.2%)	GHRT timing after cCP diagnosis: Mean 0.7 years (mean age at cCP diagnosis: 11.1±4.5/mean age at start GHRT 11.8±4.2) GHRT dose: Mean 0.6 mg/d±0.4 GHRT duration: Mean 6.1 years (mean age at start GHRT 11.8±4.2/ mean age at stop GHRT 17.9±2.9)	Outcome definition: Not reported New cases of intracranial tumors: n = 2 (0.27%)/0.18 (0.02%) (observed vs. expected) New cases of extracranial tumors: n = 4 (0.54%)/6.38 (0.86%) (observed vs. expected)	Secondary neoplasms (univariate SIR): New intracranial tumors: SIR 11.2 (1.26–40.50), p = 0.035* New extracranial tumors: SIR 0.63 (0.17–1.61), p = 0.47	SB: unclear risk; reason: the original cohort of eligible cCP patients is unknown AB: low risk; reason: in this study secondary neoplasms was seen as an AE and it was mandatory to report them. As a result, although the exact number of participants with an outcome assessment was not reported, we assume that it was available for more than 75% of participants DB: unclear; reason: unknown if outcome assessors were blinded for important determinants CF: high risk; no prognostic factors (e.g., diversity in treatment) taken into account
Bell et al. [21] (2010), prospective cohort	n = 994 cCP with GHRT Control group: No control group	Not reported	Not reported	Not reported	Outcome definition Not reported Secondary neoplasms: n = 3 (0.3%) (acute lymphocytic leukemia, astrocytoma, and brain stem glioma)	Not reported	SB: unclear risk; reason: the original cohort of eligible cCP patients is unknown AB: low risk; reason: in this study secondary neoplasms was seen as an AE and it was mandatory to report them. As a result, although the exact number of participants with an outcome assessment was not reported, we assume that it was available for more than 75% of participants DB: unclear; reason: unknown if outcome assessors were blinded for important determinants CF: not applicable

cCP, childhood-onset craniopharyngioma patients; GHRT, growth hormone replacement therapy; SB, selection bias; AB, attrition bias; DB, detection bias; CF, confounding; SIR, standardized incidence ratio; AE, adverse event. Numbers presented in mean ± SDS or median [range]. *Statistically significant.

included. Of all 87, data were available for analysis. Reasons for not obtaining consent were: refusal to participate (n = 10, 10%) and not able to retrieve for obtaining consent for use of data/moved abroad (n = 7, 7%).

cCP Treatment

Of 87 cCP patients, mean age at diagnosis was 7.39 years ±3.67 and mean age at follow-up was 14.19 years ±4.98. Of all, 26 (29.9%) had been treated with eCD/F, 24 patients (27.6%) with LR, 14 (16.1%) with NTR, and 22 (25.3%) with GTR. One patient was given a wait and see policy. Seven patients (8.0%) received local RT immediately after their first surgery. Another 33 patients (37.9%) received RT at time of progression/recurrence. Of the 65 patients with limited surgery (wait and see, eCD/F, LR, or NTR), 7 (10.8%) patients received RT directly following first surgery, and 31 (47.7%) for tumor progression/recurrence at follow-up with a mean delay of 2.90 years ±2.71 after cCP diagnosis. Twenty-seven cCP (41.5%) had not received any RT at last moment of follow-up, after a mean follow-up time of 4.71 years ±3.39. Of the 22 patients who were given GTR, 2 patients (9.0%) received RT at follow-up, with a mean delay of 2.03 years ±0.75. Interferon alpha for cystic cCP was given in 11.5% as initial therapy, and in 6.9% during follow-up at time of cyst growth. None of the patients died or developed a secondary tumor during follow-up.

Tumor Progression/Recurrence

Of the 87 patients, 53 patients (60.9%) had one or more tumor progression or recurrent events after a mean period of 1.09 years ±0.92 (after diagnosis) that resulted in additional treatment. Of these, 48 (55.2%) cCP patients had tumor progression and 5 (5.7%) tumor recurrence. In total, there were 100 events of progression/recurrences requiring treatment in these 53 patients. In 56.0% surgery was the treatment of first choice, in 25.0% radiotherapy, in 8.0% surgery plus RT, in 10.0% interferon alpha, and in one event tocilizumab. Of the 40 patients treated with radiotherapy (seven immediately after initial treatment, 33 at follow-up), 11 patients (27.5%) developed a progression/recurrence event after RT requiring treatment.

Children who received limited surgery with RT (n = 38) had significant lower tumor/progression rates than those without RT (n = 27) (26.3% vs. 51.9%, p = 0.036). Thirteen patients who had been given limited surgery (eCD/F, LR, or NTR) without RT had no tumor progression after a mean follow-up time 4.24 years ±4.22. The 5- and 10-year progression/recurrence-free survival rates were both 32.3% ± 5.6 (Fig. 2a).

GHRT and cCP Progression/Recurrence

In total 78/87 (89.7%) cCP were diagnosed with GHD, of whom 75 (86.2%) received GHRT at any point during follow-up. In 1 patient using GHRT, the starting date of GHRT was unknown and was therefore excluded for further analysis. One patient had already started GHRT before cCP diagnosis. At cCP diagnosis, GHRT was paused for 5 months and restarted after no signs of tumor residue.

No difference was found in progression/recurrence rate amongst patients receiving GHRT versus patients who did not; 61.3% versus 58.3%, respectively. Of 74 patients receiving GHRT, 19/74 (25.7%) developed progression/recurrence before starting GHRT, 10/74 (13.5%) developed multiple progressive events, both before starting and during GHRT, and 16/74 (21.6%) patients developed progressive disease only during GHRT. PFS/recurrence survival did not differ between patients with or without GHRT (p = 0.416) (Table 4).

Timing of GHRT

Of 74 patients who received GHRT, 39 patients (44.8%) started with GHRT within 1 year after cCP diagnosis (group A, mean start GHRT at 7.46 months ±2.97), and 35 patients (40.2%) started GHRT after 1 year or later (group B, mean start GHRT at 30.91 months ±18.02).

Differences in cCP treatment between the patients who started GHRT within 1 year and those who started after 1 year were: eCD/F or LR as first choice of treatment (41.0% vs. 68.6%), radiotherapy as part of initial treatment (7.7% vs. 11.4%), and radiotherapy as treatment for tumor progression/recurrence before the start of GHRT (n = 67) (0.0% vs. 38.7%). Duration of GHRT did not differ between the two groups (group A: 5.46 years [IQR 2.08–9.34] vs. group B: 4.66 years [IQR 1.92–7.48] p = 0.512).

In group A, 4/39 (10.3%) cCP patients had developed tumor progression/recurrence before start GHRT compared to 25/35 (71.4%) in group B. Median time from cCP diagnosis until first tumor progression/recurrence was 1.50 years [0.13–4.36] in group A and 1.03 years [0.25–2.96] in group B. During GHRT, 16/39 (41.0%) of patients in group A developed tumor progression/recurrence versus 10/35 (28.6%) in group B. Median number of tumor progression/recurrence events per patient during GHRT was not different between the two groups (group A: 1.0 [1–3] vs. group B: 1.5 [1–4], p = 0.241).

Using landmark analysis with the landmark point set at 6 months, 1 year (Fig. 2b), or 1.5 years, progression/recurrence-free survival did not differ between cCP who started with GHRT before the landmark versus

Table 4. Patient characteristics at diagnosis and follow-up

	GHRT n = 75 (86.2)*	No GHRT n = 12 (13.8)	p value	Start GHRT 0–12 months n = 39 (52.7)	Start GHRT >12 months n = 35 (47.3)	p value
Sex						
Female	44 (59.5)	6 (50.0)	0.538	24 (61.5)	20 (57.1)	0.701
Age at Dx (years)	7.5 [1.0–15.0]	6.0 [1.9–16.9]	0.375	8.2±3.9	6.5±3.1	0.036*
Age at FU (years)	14.7±4.9	10.9±4.5	0.017*	14.8±5.2	14.4±4.3	0.710
Follow-up time (years)	6.7 [1.0–18.1]	3.4 [0.7–10.7]	0.022*	6.2 [1.1–18.1]	7.3 [1.1–16.0]	0.144
Tumor type						
Cyst	28 (37.3)	7 (58.3)	0.274	13 (33.3)	15 (42.9)	0.579
Solid	1 (1.3)	0 (0.0)		0 (0.0)	1 (2.9)	
Mixed	39 52.0)	3 (25.0)		22 (56.4)	17 (48.6)	
Unknown	7 (9.3)	2 (16.7)		4 (10.3)	2 (5.7)	
Extent of surgery at Dx						
None	1 (1.3)	0 (0.0)	0.140	1 (2.6)	0 (0.0)	0.026*
eCD/F	20 (26.7)	6 (50.0)		9 (23.1)	11 (31.4)	
LR	20 (26.7)	4 (33.3)		6 (15.4)	13 (37.1)	
NTR	12 (16.0)	2 (16.7)		6 (15.4)	6 (17.1)	
Total resection	22 (29.3)	0 (0.0)		17 (43.6)	5 (14.3)	
Adjuvant RT (at Dx)	7 (9.3)	0 (0.0)		3 (7.7)	4 (11.4)	
RT received at FU	31 (41.3)	2 (16.7)	0.123	9 (23.1)	16 (60.0)	0.001*
RT mode						
Protons	21 (55.3)	1 (50.0)	0.704	8 (66.7)	13 (52.0)	0.926
Photons	7 (18.4)	0 (0.0)		2 (16.7)	15 (20.0)	
Unknown	10 (26.3)	1 (50.0)		2 (16.7)	7 (28.0)	
Interferon α at Dx/FU	8 (10.7)	4 (33.3)	0.057	2 (5.1)	6 (17.1)	0.139
Duration of GHRT (years)	4.9 [0.0–17.1]	–	–	5.5 [0.1–17.2]	4.7 [0.0–13.7]	0.512
Tumor progression/recurrence						
Total follow-up time	46 (61.3)	7 (58.3)	1.000	17 (43.6)	28 (80.0)	0.001*
Before GHRT	29 (39.2)	–	–	4 (10.3)	25 (71.4)	<0.001*
During GHRT	26 (35.1)	–	–	16 (4,107)	10 (28.6)	0.263

Numbers are presented as n (%), mean ± standard deviations score, or median [range]. GHRT, growth hormone replacement therapy; mo, months; Dx, diagnosis; FU, follow-up; RT, radiotherapy. *Of 1 patient starting date of GHRT was missing.

cCP who started with GHRT after the landmark ([n = 70] p = 0.894, [n = 55] p = 0.073, and [n = 49] p = 0.244, respectively). Multivariate Cox regression (with landmark set at 1 year from cCP diagnosis), including starting time of GHRT and limited surgery (eCD/F, LR, or NTR), showed a trend toward increased risk of limited surgery for tumor progression (HR 2.81 95% CI 0.95–8.27, p = 0.061).

Of the 39 cCP starting GHRT within the year, 14 (16.1%) had started GHRT within 6 months after cCP diagnosis and 25 (28.7%) had started between 6 months and 1 year. Of the 35 cCP starting GHRT after 1 year, 17 (19.5%) started between one and 2 years after cCP diagnosis, and 18 (20.7%) started after 2 years or later. When these four GHRT groups were compared, a statistically significant increasing progression/recurrence rate was found associated with a later start of GHRT (GHRT started <6 months: 50.0%, GHRT started 6 months–1 year: 40.0%, GHRT started 1–2 years: 58.8%, GHRT start >2 years: 100.0%, p < 0.001). Tumor progression/recurrence during GHRT (excluding patients treated with radiotherapy before start of GHRT, n = 19) was not different: 53.8%, 34.8%, 33.3%, and 57.1%, respectively (p = 0.541).

In the multivariate Cox regression, using timing of GHRT as a time-dependent covariate, extent of surgery at diagnosis (eCD/F, LR, or NTR) was a significant risk factor for developing progression/recurrence (HR 8.09 CI 95% 3.09–21.21). Radiotherapy at moment of diagnosis was a protective factor for tumor progression/recurrence (HR 0.27 95% CI 0.08–0.89). No increased risk for developing progression/recurrence was found for GHRT, timing of GHRT, or GHRT duration (Table 5).

Other Endocrine Deficiencies

Of the 87 patients, 87.4% had been diagnosed with thyroid-stimulating hormone deficiency, 75.9% with adrenocorticotropic hormone deficiency, 49.4% with gonadotrophin deficiency, 73.6% with diabetes insipidus, and 8.0% with central precocious puberty. All patients had received adequate substitution therapy with levo-thyroxine, hydrocortisone, sex steroids, or desmopressin when indicated. Of the 7 patients (8.0%) diagnosed with central precocious puberty, all had received GnRH analogues.

Discussion

Delay in treatment of GHD in childhood may severely affect final height, especially when this occurs during pubertal development [39]. In addition, GHD may have detrimental effect on metabolic health, which is of special importance in cCP with hypothalamic damage [40]. For fear of tumor progression or recurrence, treatment with GHRT, and its timing, may be a subject of discussion between the oncologist and the parents [41]. The results of this systematic review of current literature combined with the results of our own cohort studys, suggest that GHRT in children treated for cCP does not increase the risk for overall mortality, progression or recurrent disease, independent of timing of GHRT.

In one study, a statistically significant increased risk for a secondary intracranial tumor compared to age- and sex-specific general population rates was found for cCP with GHRT, with a trend toward radiotherapy as confounding risk factor [38]. Other large cohort studies have shown that GHRT in cancer survivors does not increase the risk for secondary tumors or recurrence, but that the risk for secondary tumors is mainly related to the given radiotherapy [42, 43]. Taking these reassuring data into account, it may even be advocated, from a physiological point of view, that GHRT should be given to all children with GHD from time of diagnosis to optimize metabolic outcome, irrespective of underlying disease. Future research, including prospective designs, should address the possibility of more early initiation of GHRT.

The data provided in this manuscript will help to adequately balance the benefits and risks for starting GHRT in children with cCP. Benefits of GHRT in children with GHD are improvement of final height, bone strength, and body composition including BMI [22, 44–49]. In cCP patients, quality of life is mainly disturbed due to hypothalamic-pituitary dysfunction, resulting in hypothalamic obesity [1]. Improving body composition and BMI in these children is thus of special importance and early initiation of GHRT may positively influence this outcome. Data supporting the effects of GHRT on body composition in children with hypothalamic obesity is, however, inconsistent, but it must be considered that hypothalamic obesity is a highly complex disease with many factors contributing to its etiology and solely evaluating the effect of GHRT is, therefore, very challenging [47, 50, 51].

Because of the advocated shifting in treatment regimen from GTR to limited surgery, the number of cCP patients with residual disease is expected to increase. The argument favoring LR is the increased risk for hypothalamic dysfunction associated with complete resection [52]. Hypothalamic damage is the most important adverse outcome impacting QoL and LR has shown to be preventive for hypothalamic damage to some degree [53, 54].

Of our cohort, 48/89 (53.9%) had tumor progression and 5/89 (5.6%) had tumor recurrence requiring treatment. Compared to literature, our progression/recurrence rate seems to be higher, with overall tumor progression/recurrence rates reported from 4.2% to 50.0% [21, 23–28, 30, 31, 33–35, 38]. This difference may be explained by the fact that, in our cohort, only 25.3% of the patients received GTR. Not surprisingly, in our multivariate analysis, limited surgery was indeed a risk factor for tumor progression/recurrence.

The optimal timing of radiotherapy in cCP also remains a matter of debate [55]. To wait with radiotherapy until disease progression can be beneficial and even crucial in young children who are still in the essential process of brain development. In this regard, the possible beneficial effects of radiotherapy (tumor control) must be balanced against its possible adverse effects, such as additional hypothalamic-pituitary damage, cognitive decline, vascular injuries, and secondary neoplasms [56, 57]. With this respect, an important observation in our cohort was the fact that of the 65 patients who did not receive GTR, 27 (41.5%) had not received additional radiotherapy at last moment of follow-up. Of these, 13/27 (48.1%) did not develop any tumor progression event (mean follow-up time 4.24 years ±4.22), of which 8/13 (61.5%) had received GHRT. The other 14/27 (51.9%) cCP developed tumor progression, of which 9/14 (64.3%) had received GHRT. On the other hand, 26.3% of patients treated with LR and additional radiation (n = 38), still developed a recurrent disease, which has also been reported by others [29, 58, 59]. Possibly, the margins of the radiation field may have contributed to this rate and this should be evaluated in future research.

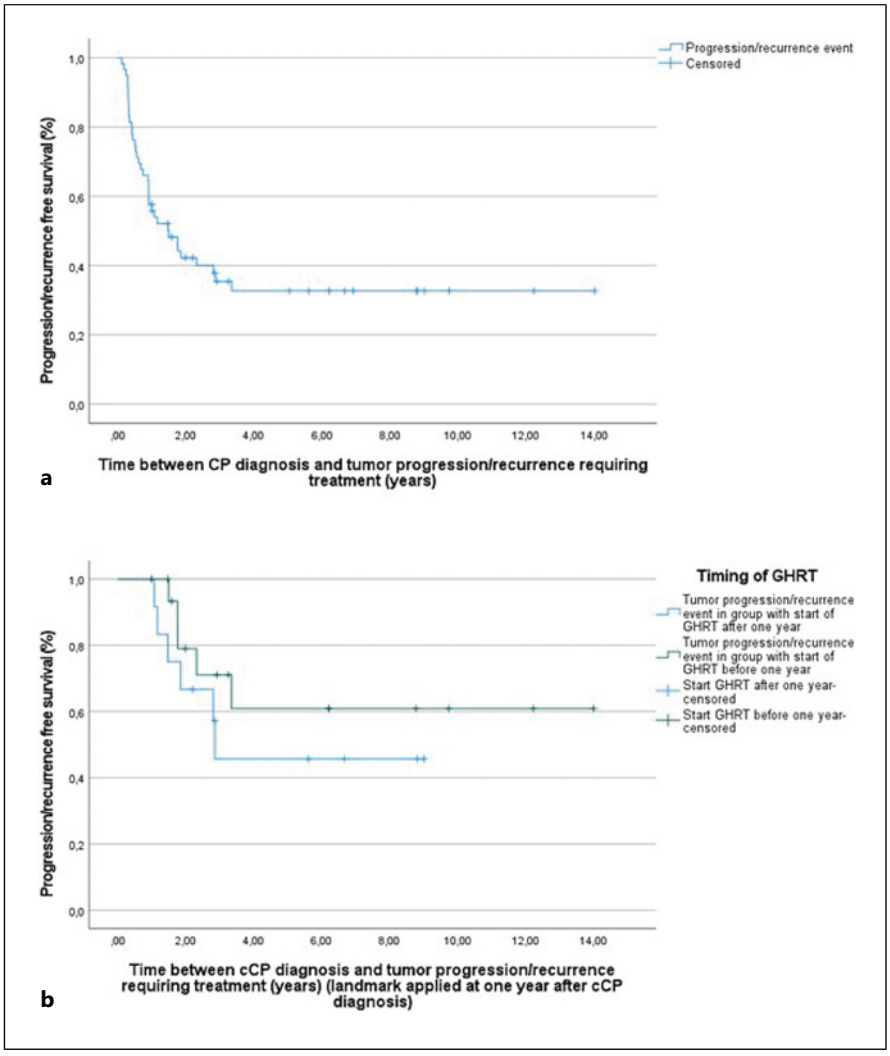

Fig. 2. a Kaplan-Meier curve of progression/recurrence-free survival in cCP. **b** Kaplan-Meier curve of progression/recurrence-free survival in cCP who started with GHRT within 1 year versus after 1 year of diagnosis (with landmark applied at 1 year after cCP diagnosis). cCP, childhood-onset craniopharyngioma; GHRT, growth hormone replacement therapy.

The quality of the evidence we found by our systematic review, to answer the question on optimal timing of GHRT, is low. The one study we found did not report an increase in progression/recurrence-free survival with different starting times of GHRT after cCP diagnosis in a univariate analysis, but multivariate analysis was lacking [26, 29]. In our cohort, we found no difference in PFS between cCP patients who were given GHRT <1 year when compared to after 1 year. It was noticed, however, that the children who started GHRT >1 year after diagnosis, more often had developed tumor progression/recurrence already before starting GHRT (group B). These progression/recurrence events before starting GHRT may have been the reason not to start GHRT and may thus be considered as an inherent bias. Therefore, we performed a landmark analysis excluding patients with progression/recurrence in the first year after diagnosis. Using this analysis, we did not identify any differences between the groups. Unfortunately, we were not able to perform an extensive cox regression with multiple covariates, as the number of events were limited. Future research should focus on prospective designs, starting GHRT irrespective of CP rest/regrowth or recurrence at different time intervals.

The results of the literature search and our cohort studys have inherent limitations. It must be acknowledged that the quality of the studies that were included in the systematic review was limited; most of the studies did not include an adequate control group (i.e., cCP patients with GHD but without GHRT), or adequate risk analysis (i.e., taking into account all relevant prognostic factors). In addition, there was risk of bias and the power of the study was often limited,

Table 5. Risk factors for tumor progression/recurrence

	Hazard ratio	95% Confidence interval			*p* value
		lower		upper	
Limited surgery[a] (yes/no)	8.09	3.09	–	21.21	<0.001*
Radiotherapy at diagnosis (yes/no)	0.27	0.08	–	0.89	0.032*
Timing of GHRT (in years)	1.00	0.89	–	1.12	0.959
Use of GHRT (yes/no)	1.38	0.53	–	3.59	0.507
Duration of GHRT (in years)	1.00	0.93	–	1.07	0.940

Multivariable cox regression model with timing of GHRT as a time-dependent covariate was used to generate estimates of relative risk for tumor progression/recurrence in children with craniopharyngioma. GHRT, growth hormone replacement therapy; cCP, childhood-onset craniopharyngioma. [a]Limited surgery consisted of either: wait and see policy, eCD/F, LR, or NTR within the first 3 months after diagnosis. *Statistically significant.

due to small sample size. Underreporting of complications cannot be precluded, as in most registries, data are based on information provided by the attending physician. Moreover, initiation of GHRT in cCP is dependent on the judgement of the physician, as individuals in cohorts are not randomized. Patients with prior recognized risk factors, such as former progression/recurrence, could have been excluded from receiving GHRT. Therefore, incidence of adverse events may have been underestimated. It must be acknowledged, that there is a lack of long-term data on safety of GHRT in the literature search, as well as in our cohort studys. Future studies should therefore aim on a long-term registry design or perform data linkage studies; however, it may take many years for such studies to find moderate effects. Next, in our review, data of nine studies were based on five different multinational observational studies, thus possible overlap in patients must be taken into account when interpreting these results. Although the results of our cohort analysis are in line with the existing literature, it must be noted that the distribution between patients with GHRT versus no GHRT was very skewed, conclusions should, therefore, be drawn with caution.

The strengths of our review and cohort studys include the elaborate literature search, the dual assessment of obtained articles, and the high-quality assessment of timing of GHRT. The data provided will contribute to optimally balance the benefits against the potential risks for starting GHRT in cCP. Future studies are needed with preferably, large prospective randomized controlled trials, also focusing on the newest recommendation from the Growth Hormone Research Society stating that GH may be started as early as 3 months after cCP diagnosis.

In conclusion, the available evidence suggests that there is no increased risk of overall mortality, tumor progression/recurrence, or secondary neoplasms in cCP patients after starting GHRT and no effect of timing of GHRT. Although these results are reassuring, it must be kept in mind that the quality of the evidence is mostly low. Careful long-term surveillance after starting GHRT in cCP patients is crucial and there is need for prospective studies. The benefits and possible harms of commencing GHRT and its timing should be a shared decision of the health care professional together with the patient and the parents based on individual arguments, such as age, longitudinal growth, pubertal stage, presence and worries of tumor residue, and metabolic state.

Statement of Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Given the retrospective character of the data analysis, the local Institutional Review Board (METC Utrecht, the Netherlands) decided that the Act on Medical Research Involving Human Subjects did not apply and provided a waiver (20-640/C). Written informed consent was obtained for participation in this study. Written informed consent was obtained from parents/legal guardians for all patients aged under 18 years and patient itself (if age 12 and up) to participate in the study.

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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Author Contributions

van Schaik J conceptualized and designed the study; contributed to the acquisition, analysis, and interpretation of the data; drafted the initial manuscript; and reviewed and revised the manuscript. Kormelink E and Kabak E contributed to the acquisition, analysis, and interpretation of the data and reviewed and revised the manuscript. van Dalen E.C., Schouten-van Meeteren A.Y.N., de Vos-Kerkhof E., Bakker B., Fiocco M., Hoving E.W., and Tissing W.J.E. contributed to the analysis and interpretation of the data and reviewed and revised the manuscript. Dr. Hanneke van Santen conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Data Availability Statement

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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