Hypothalamic-pituitary injury after childhood cancer and central nervous system tumors

risk factors, course & consequences

Laura van Iersel

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Risk Factors, Course and Consequences

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Colophon

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Risk Factors, Course and Consequences

Hypothalame-hypofysaire schade na behandeling voor kinderkanker en tumoren in het centrale zenuwstelsel

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(met een samenvatting in het Nederlands)

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Contents

1

General introduction

General introduction

The survival rate of childhood cancer has substantially improved over the last decades. The overall 5-year survival rate from childhood cancer is estimated at 80%.[1] Childhood cancer survivors have lifelong increased risks for developing chronic health conditions, which due to their occurrence several months to years after the completion of cancer treatments are termed late effects.[2] This has resulted in greater emphasis on adequate screening and early intervention to optimize long-term health outcomes in this vulnerable population.

Endocrine disorders are among the most common late effects and it is estimated that up to 40-50% of survivors will develop an endocrine disorder during their lifetime.[3] Endocrine disorders include hypothalamic-pituitary (HP), thyroid, adrenal and gonadal disorders, obesity, diabetes mellitus and the metabolic syndrome. This thesis focusses primarily on HP disorders and male gonadal dysfunction.

Hypothalamic function

The hypothalamus, located at the base of the third ventricle below the thalamus, is a point of interaction for two physical systems: the nervous system and endocrine system. The hypothalamus consists of many different nuclei with a variety of functions to maintain homeostasis.[4] In the preoptic and supraoptic area, supraoptic, paraventricular and suprachiasmatic nuclei are responsible of hormonal secretion and circadian rhythm control. The middle or tuberal region contains the ventromedial and arcuate nuclei, responsible for feeding behavior. The posterior or mammillary region includes the posterior nuclei and mammillary bodies that regulate body temperature and interact with the limbic system.

The hypothalamic-pituitary axes

The hypothalamus and pituitary gland are connected by the hypothalamic-hypophyseal tract, a network of specialized neurons and vessels. The pituitary gland is encased in the sella turcica of the sphenoid bone and is divided in two parts: an anterior lobe or adenohypophysis and a posterior lobe, the neurohypophysis.[5] The adenohypophysis includes distinct cell types which secrete hormones in response to hypothalamic releasing hormones. The latter travel from the hypothalamus to the adenohypophysis via the hypothalamic-hypophyseal portal system. The main hypothalamic releasing hormones are growth hormone releasing hormone (GHRH), thyrotropin releasing hormone (TRH), corticotropin releasing hormone (CRH) and gonadotropin releasing hormone (GnRH, Figure 1). The neurohypophysis is primarily constituted of axonal terminals of hypothalamic-hypophyseal tract neurons. Oxytocin and anti-diuretic hormone (ADH) are produced in the hypothalamic nuclei where these neurons originate; the neurohypophysis serves to store and release oxytocin and ADH into the bloodstream.

Hypothalamic-pituitary-end organ function

The interaction between the hypothalamus, pituitary and end organ gland is mainly regulated by negative feedback loops. Hormones secreted by the end organ gland bind to receptors in the hypothalamus and/or pituitary triggering a response that decreases the secretion of releasing and /or stimulating hormones. Thus, hormones decrease their own rate of secretion, which allows maintenance of hormone levels within narrow ranges.

GHRH stimulates the GH producing somatotropic cells in the adenohypophysis. Depending on the target organ, GH may act directly via binding on its own receptor or indirectly via stimulation of insulin-like growth factor 1 (IGF-1), which is primarily produced in the liver.[6] GH is secreted throughout the entire lifespan; its secretion declines with age.[7] IGF-1 promotes cell survival, proliferation and differentiation. For example, linear growth is stimulated by IGF-1 through proliferation of chondrocytes at the epiphyseal plates that enhance bone growth. Other actions of IGF-1 and GH include effects on lipid, glucose and protein metabolism: they stimulate lipolysis in adipose tissue, decrease glucose uptake and stimulate gluconeogenesis in the liver, and stimulate the uptake of amino acids in the muscles.[8]

TRH stimulates thyroid stimulating hormone (TSH) producing thyrotropic cells in the adenohypophysis. In turn, TSH stimulates the thyroid gland to synthesize the thyroid hormones thyroxine (T4) and triiodothyronine (T3). Although T3 is more active than T4, T4 is produced by the thyroid gland in much greater amounts than T3. Most T3 is produced in target organ tissues by conversion of T4 into active T3 via deiodination.[9] Thyroid hormones play an important role in bone and nervous system development. In addition, thyroid hormones regulate the basal metabolic rate, stimulate lipolysis and gluconeogenesis, and reduce serum cholesterol and triglycerides levels.[10]

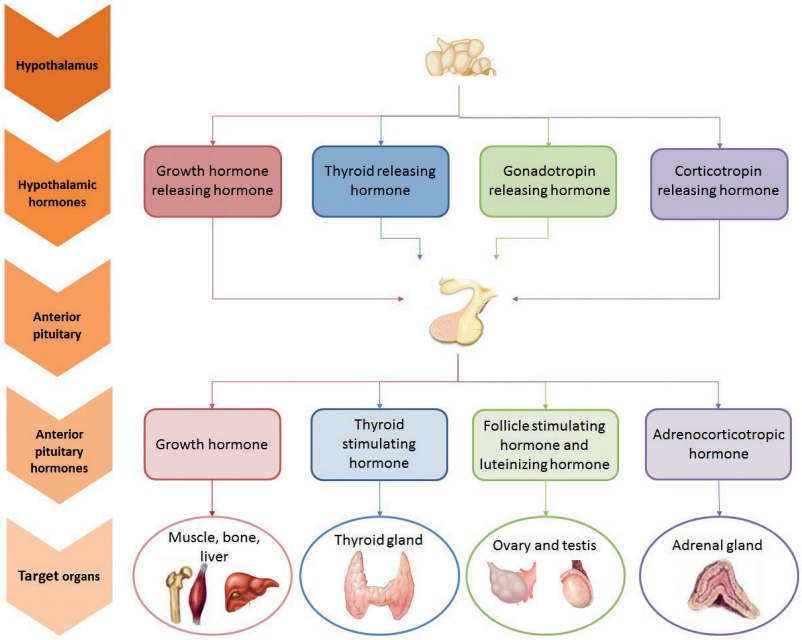
CRH stimulates adrenocorticotropic hormone (ACTH) secretion by the corticotropic cells of the adenohypophysis. The target tissue of ACTH is the adrenal cortex which in turn produces glucocorticoids from the zona fasciculata and androgens from the zona reticularis. The produced androgens supplement the gonadal androgens and are converted in tissues to testosterone and estrogens. The hypothalamic-pituitary axis increases CRH secretion in response to stressful stimuli.[11] Glucocorticoids, such as cortisol, mediate a variety of metabolic effects in response to stressors such as stimulating protein catabolism and gluconeogenesis, and inhibiting peripheral glucose uptake.

The active inhibition of GnRH release prevents the onset of puberty during childhood. Puberty is initiated when the hypothalamus starts to secrete pulses of GnRH. The exact trigger that determines the timing of pulsatile GnRH secretion by the hypothalamus is unknown. It seems to vary according to gender and depend on other parameters such as genetic factors,

environmental influences, and nutrition status.[12] GnRH in turn stimulates, gonadotropin, i.e. luteinizing hormone (LH) and follicle-stimulating hormone (FSH), production and secretion by the gonadotropic cells of the adenohypophysis. In boys, FSH stimulates germ cell production and LH stimulates testosterone secretion by the testes. In girls, FSH stimulates the growth of ovarian follicles while LH stimulates ovulation and development of the corpus luteum. In turn, the ovaries produce sex steroid hormones, including estrogen and progesterone. The GnRH-stimulated gonadotropin release with subsequent rise in testosterone or estrogen concentrations promotes the development of secondary sexual characteristics in boys (e.g. facial and body hair, deepening of the voice, enlargement of the penis) and girls (e.g. breast development, body hair, widening of the hips and changes in fat distribution), and linear growth.

Oxytocin and ADH are produced in the hypothalamus, but secreted by the neurohypophysis.[13] Oxytocin plays an important role in contraction of the uterus during childbirth and lactation, but also influences social behavior and learning. ADH is important for regulation of fluid and electrolyte balance. ADH increases free water reabsorption in the kidney in order to maintain adequate hydration. It also promotes vasoconstriction; both processes result in increased blood pressure.

Figure 1. Physiology of the hypothalamic-anterior-pituitary axes



Endocrine disorders after treatment of childhood cancer

Hypothalamic dysfunction

Hypothalamic damage may result in a wide range of disorders that affect homeostasis, including hypothalamic obesity. Acquired hypothalamic obesity is often the result of direct hypothalamic injury due to the tumor and its treatment.[14] The most striking example of severity of hypothalamic obesity is observed in patients with craniopharyngioma. This rare brain tumor arises from remnants of the Rathke's pouch, an embryonic precursor of the pituitary gland. Although this tumor is histologically benign, it causes severe morbidity due to its close anatomical relation with the optic chiasm, pituitary gland and hypothalamus.[15] Damage to the ventromedial hypothalamus results in excessive food intake and obesity, because proper integration of central and peripheral satiety hormones is disrupted.[16,17] Hypothalamic obesity is reported in up to 55% of patients treated for craniopharyngioma, and is associated with increased morbidity and mortality, and reduced quality of life.[18-21] Unfortunately, hypothalamic obesity seems resistant to pharmacological and non-pharmacological interventions, and currently no overall effective treatment strategies for this specific form of obesity exist.[22]

Hypothalamic-pituitary dysfunction

Hypothalamic-pituitary dysfunction may result in GH deficiency (GHD), TSH deficiency (TSHD), ACTH deficiency (ACTHD), LH/FSH deficiency (LH/FSHD) and central precocious puberty (CPP). A well-known risk factor for HP dysfunction is direct damage of the HP region by the tumor itself or surgical resection. Up to 54.8% of children diagnosed with low-grade glioma affecting the optic pathway, hypothalamus and suprasellar regions may experience one or more HP disorders.[23] A second risk factor to develop HP dysfunction includes exposure to cranial radiation therapy (RT). The prevalence of different RT-induced HP disorders varies; GHD occurs most frequently and after lower RT doses, when compared to TSHD, ACTHD and LH/FSHD.[24] GHD has been reported after RT exposure of 18-24 Gy in survivors of lymphoblastic leukemia or after total body irradiation.[25-27] In contrary, TSHD, ACTHD and LH/FSHD are reported to develop predominantly in survivors with previous HP axis exposure at doses ≥ 30 Gy.[24,28] Besides dose-dependency, RT-induced deficiencies also seem to be time-dependent; the cumulative incidence of HP dysfunction increases over time.[24,29] Survivors of childhood cancer at risk for HP dysfunction may thus require extended and lifelong endocrine screening.[30]

CPP is characterized by GnRH release by the hypothalamus at a younger-than normal age: <8 years and <9 years in girls and boys, respectively. The prevalence of organic CPP is estimated between 11.9 and 26%, depending on tumor location.[23,31,32] Although CPP has been reported after exposure to RT, tumors within or near the HP region and history of hydrocephalus are considered as the main risk factors of organic CPP.[31,33,34]

Male hypergonadotropic hypogonadism

Reduced reproductive health, including impaired spermatogenesis, testosterone deficiency, and sexual dysfunction, are frequently experienced late effects by male childhood cancer survivors.[35] In contrary to rapidly multiplying germ cells, the testosterone producing Leydig cells seem less vulnerable to damage of cancer therapies.[36] Leydig cell failure has been reported after gonadotoxic therapies, such as exposure of the testis to RT and alkylating chemotherapy.[37-40] Male hypogonadism, a potentially modifiable condition, may be a significant contributor to impaired sexual function and adverse physical outcomes in male survivors of childhood cancer.

Aims and outline of this thesis

The main aim of this thesis was to assess the prevalence, time of onset, risk factors and associated health consequences of endocrine disorders, including hypothalamic obesity (part I), HP dysfunction (part II) and male hypogonadism (part III). Improving knowledge about the presence and consequences of tumor- or tumor related endocrine damage has the potential to optimize screening strategies and to detect endocrine sequelae in a timely manner, which in turn provides targets for intervention. This may ultimately prevent or reduce the burden of HP injury after treatment of childhood neoplasms.

Part I Hypothalamic obesity following craniopharyngioma and other suprasellar tumors

In *Chapter 2*, the prevalence and risk factors associated with the development of hypothalamic (morbid) obesity in a cohort of patients with a history of craniopharyngioma are reported. *Chapter 3* includes an in-depth review of the pathophysiology of hypothalamic obesity following craniopharyngioma and other suprasellar tumors. In addition, the results of a systematic review including all intervention studies for hypothalamic obesity, are presented. The knowledge from the pathophysiology and intervention studies were combined to propose an individualized treatment algorithm for patients with acquired hypothalamic obesity. *Chapter 4* describes a pilot study that assessed the feasibility and effectivity of an individualized dietary intervention, together with extensive coaching, in children with acquired hypothalamic obesity.

Part II Hypothalamic-pituitary disorders after treatment of childhood cancer

Chapter 5 reports the prevalence, risk factor associations and clinical consequences of HP disorders in a cohort of systematically followed children with an intracranial tumor exposed to high-dose RT. In addition, safety of GH treatment in this cohort on tumor recurrence, mortality and secondary tumors was assessed. *Chapter 6* also discusses the prevalence, risk factor associations and clinical consequences of HP disorders, but in an older and larger cohort of adult childhood cancer survivors. In this cohort, all survivors underwent endocrine screening independent of treatment exposure. This enables the characterization of risk factors in individuals not exposed to RT. *Chapter 7* describes longitudinal patterns of FT4 concentrations in a cohort of childhood

brain tumor survivors treated with cranial RT. *Chapter 8* also assesses longitudinal trends of FT4 concentrations, but in a systematically followed pediatric cohort exposed to RT. In addition, we assessed risk factors and health outcomes associated with plasma FT4 concentrations. In *Chapter 9* the international harmonized surveillance recommendations for HP dysfunction for childhood, adolescent and young adult cancer survivors are presented.

Part III Male hypogonadism in survivors of childhood cancer

Chapter 10 describes the prevalence of, and risk factors for Leydig cell failure, and associated adverse health outcomes. *Chapter 11* describes the prevalence of erectile dysfunction, associated risk factors and long-term adverse health outcomes among survivors of childhood cancer. *Chapter 12* provides an overall discussion of the main findings of this thesis, including perspectives for future research.

References

1. Howlader N NA, Krapcho M, Miller D, et al (eds). SEER Cancer Statistics Review, 1975–2013. National Cancer Institute: Bethesda, MD, 2016. http://seer.cancer.gov/csr/1975_2013 (accessed February 4, 2019).
2. Robison LL, Hudson MM. Survivors of childhood and adolescent cancer: life-long risks and responsibilities. *Nat Rev Cancer.* 2014;14(1):61-70.
3. Mostoufi-Moab S, Seidel K, Leisenring WM, et al. Endocrine Abnormalities in Aging Survivors of Childhood Cancer: A Report From the Childhood Cancer Survivor Study. *J Clin Oncol.* 2016;34(27):3240-3247.
4. Gao Y, Sun T. Molecular regulation of hypothalamic development and physiological functions. *Mol Neurobiol.* 2016;53(7):4275-4285.
5. Nussey S, Whitehead S. *Endocrinology: An Integrated Approach*. Oxford, 2001.
6. Rozario KS, Lloyd C, Ryan F. GH and IGF-1 Physiology In Childhood. In: De Groot LJ, Chrousos G, Dungan K, et al., eds. *Endotext*. South Dartmouth (MA)2000.
7. Giustina A, Veldhuis JD. Pathophysiology of the neuroregulation of growth hormone secretion in experimental animals and the human. *Endocr Rev.* 1998;19(6):717-797.
8. Moller N, Jorgensen JO. Effects of growth hormone on glucose, lipid, and protein metabolism in human subjects. *Endocr Rev.* 2009;30(2):152-177.
9. Bianco AC, Salvatore D, Gereben B, Berry MJ, Larsen PR. Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine selenodeiodinases. *Endocr Rev.* 2002;23(1):38-89.
10. Mullur R, Liu YY, Brent GA. Thyroid hormone regulation of metabolism. *Physiol Rev.* 2014;94(2):355-382.
11. Smith SM, Vale WW. The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress. *Dialogues Clin Neurosci.* 2006;8(4):383-395.
12. Abreu AP, Kaiser UB. Pubertal development and regulation. *Lancet Diabetes Endocrinol.* 2016;4(3):254-264.
13. The Neurohypophysis: Endocrinology of Vasopressin and Oxytocin. In: Feingold KR, Anawalt B, Boyce A, et al., eds. *Endotext*. South Dartmouth (MA)2000.
14. Lustig RH, Post SR, Srivannaboon K, et al. Risk factors for the development of obesity in children surviving brain tumors. *J Clin Endocrinol Metab.* 2003;88(2):611-616.
15. Karavitaki N, Brufani C, Warner JT, et al. Craniopharyngiomas in children and adults: systematic analysis of 121 cases with long-term follow-up. *Clin Endocrinol (Oxf).* 2005;62(4):397-409.
16. King BM. The rise, fall, and resurrection of the ventromedial hypothalamus in the regulation of feeding behavior and body weight. *Physiol Behav.* 2006;87(2):221-244.
17. Hoffmann A, Postma FP, Sterkenburg AS, Gebhardt U, Muller HL. Eating behavior, weight problems and eating disorders in 101 long-term survivors of childhood-onset craniopharyngioma. *J Pediatr Endocrinol Metab.* 2015;28(1-2):35-43.
18. Cohen M, Guger S, Hamilton J. Long term sequelae of pediatric craniopharyngioma - literature review and 20 years of experience. *Front Endocrinol (Lausanne).* 2011;2:81.
19. Sterkenburg AS, Hoffmann A, Gebhardt U, Warmuth-Metz M, Daubenbuchel AM, Muller HL. Survival, hypothalamic obesity, and neuropsychological/psychosocial status after childhood-onset craniopharyngioma: newly reported long-term outcomes. *Neuro Oncol.* 2015;17(7):1029-1038.
20. Haliloglu B, Atay Z, Guran T, et al. Risk factors for mortality caused by hypothalamic obesity in children with hypothalamic tumours. *Pediatr Obes.* 2016;11(5):383-388.
21. Muller HL, Bruhnken G, Emser A, et al. Longitudinal study on quality of life in 102 survivors of childhood craniopharyngioma. *Childs Nerv Syst.* 2005;21(11):975-980.
22. Wang KW, Chau R, Fleming A, et al. The effectiveness of interventions to treat hypothalamic obesity in survivors of childhood brain tumours: a systematic review. *Obes Rev.* 2017;18(8):899-914.

23. Gan HW, Phipps K, Aquilina K, Gaze MN, Hayward R, Spoudeas HA. Neuroendocrine Morbidity After Pediatric Optic Gliomas: A Longitudinal Analysis of 166 Children Over 30 Years. *J Clin Endocrinol Metab.* 2015;100(10):3787-3799.
24. Chemaitilly W, Li Z, Huang S, et al. Anterior hypopituitarism in adult survivors of childhood cancers treated with cranial radiotherapy: a report from the St Jude Lifetime Cohort study. *J Clin Oncol.* 2015;33(5):492-500.
25. Brennan BM, Rahim A, Mackie EM, Eden OB, Shalet SM. Growth hormone status in adults treated for acute lymphoblastic leukaemia in childhood. *Clin Endocrinol (Oxf).* 1998;48(6):777-783.
26. Bjork J, Link K, Erfurth EM. The utility of the growth hormone (GH) releasing hormone-arginine test for diagnosing GH deficiency in adults with childhood acute lymphoblastic leukemia treated with cranial irradiation. *J Clin Endocrinol Metab.* 2005;90(11):6048-6054.
27. Brennan BM, Shalet SM. Endocrine late effects after bone marrow transplant. *Br J Haematol.* 2002;118(1):58-66.
28. Laughton SJ, Merchant TE, Sklar CA, et al. Endocrine outcomes for children with embryonal brain tumors after risk-adapted craniospinal and conformal primary-site irradiation and high-dose chemotherapy with stem-cell rescue on the SJMB-96 trial. *J Clin Oncol.* 2008;26(7):1112-1118.
29. Merchant TE, Rose SR, Bosley C, Wu S, Xiong X, Lustig RH. Growth hormone secretion after conformal radiation therapy in pediatric patients with localized brain tumors. *J Clin Oncol.* 2011;29(36):4776-4780.
30. Sklar CA, Antal Z, Chemaitilly W, et al. Hypothalamic-Pituitary and Growth Disorders in Survivors of Childhood Cancer: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2018;103(8):2761-2784.
31. Chemaitilly W, Merchant TE, Li Z, et al. Central precocious puberty following the diagnosis and treatment of paediatric cancer and central nervous system tumours: presentation and long-term outcomes. *Clin Endocrinol (Oxf).* 2016;84(3):361-371.
32. Armstrong GT, Liu Q, Yasui Y, et al. Long-term outcomes among adult survivors of childhood central nervous system malignancies in the Childhood Cancer Survivor Study. *J Natl Cancer Inst.* 2009;101(13):946-958.
33. Brauner R, Czernichow P, Rappaport R. Precocious puberty after hypothalamic and pituitary irradiation in young children. *N Engl J Med.* 1984;311(14):920.
34. Clement SC, Schouten-van Meeteren AY, Boot AM, et al. Prevalence and Risk Factors of Early Endocrine Disorders in Childhood Brain Tumor Survivors: A Nationwide, Multicenter Study. *J Clin Oncol.* 2016;34(36):4362-4370.
35. Kenney LB, Cohen LE, Shnorhavorian M, et al. Male reproductive health after childhood, adolescent, and young adult cancers: a report from the Children's Oncology Group. *J Clin Oncol.* 2012;30(27):3408-3416.
36. Sklar C. Reproductive physiology and treatment-related loss of sex hormone production. *Med Pediatr Oncol.* 1999;33(1):2-8.
37. 37. Sklar CA, Robison LL, Nesbit ME, et al. Effects of radiation on testicular function in long-term survivors of childhood acute lymphoblastic leukemia: a report from the Children Cancer Study Group. *J Clin Oncol.* 1990;8(12):1981-1987.
38. 38. Howell SJ, Radford JA, Ryder WD, Shalet SM. Testicular function after cytotoxic chemotherapy: evidence of Leydig cell insufficiency. *J Clin Oncol.* 1999;17(5):1493-1498.
39. 39. Greenfield DM, Walters SJ, Coleman RE, et al. Prevalence and consequences of androgen deficiency in young male cancer survivors in a controlled cross-sectional study. *J Clin Endocrinol Metab.* 2007;92(9):3476-3482.
40. 40. Isaksson S, Bogefors K, Stahl O, et al. High risk of hypogonadism in young male cancer survivors. *Clin Endocrinol (Oxf).* 2018;88(3):432-441.

2

The development of hypothalamic obesity in craniopharyngioma patients: a risk factor analysis in a well-defined cohort

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Abstract

Background

Hypothalamic obesity (HO) is a major concern in patients treated for craniopharyngioma (CP). The influence of degree of resection on development of HO, event-free survival (EFS) and neuroendocrine sequelae is an issue of debate.

Procedure

A retrospective cohort consisting of all CP patients treated between 2002 and 2012 in two university hospitals was identified. Multivariable logistic regression was used to study the associations between preoperative BMI, age at diagnosis, tumor volume, performed surgical resection, and presence of HO at follow-up.

Results

Thirty-five patients (21 children and 14 adults) were included. Median follow-up time was 35.6 months (4.1-114.7). Four patients were obese at diagnosis. HO was present in 19 (54.3%) patients at last follow-up of whom eight were morbidly obese. Thirteen (37.1%) patients underwent partial resection (PR) and 22 (62.9%) gross total resection (GTR). GTR was related to HO (OR 9.19, 95% CI 1.43-59.01), but for *morbid* HO, obesity at diagnosis was the only risk factor (OR 12.92, 95% CI 1.05-158.73). EFS in patients after GTR was 86%, compared to 42% after PR (log-rank 9.2, $P = 0.003$). Adjuvant radiotherapy after PR improved EFS (log-rank 8.2, $P = 0.004$). Panhypopituitarism, present in 15 patients, was mainly seen after GTR.

Conclusions

HO is less frequent after PR than after GTR, but PR cannot always prevent the development of morbid obesity in patients with obesity at diagnosis. PR reduces the occurrence of panhypopituitarism. When developing a treatment algorithm, all these factors should be considered.

Introduction

Craniopharyngioma (CP) is a rare tumor, with a bimodal distribution in children (5-14 years) and adults (50-74 years).[1] Histologically this tumor is benign (WHO grade I) with the adamantinomatous histology more frequently seen in the younger patients and the papillary subtype in adult and elderly patients.[2] Despite its benign histological characteristics, CP may cause severe morbidity, due to its close anatomical relation with the optic chiasm, pituitary gland, and hypothalamus. One of the most important long-term adverse effects is hypothalamic obesity (HO), which has a major negative impact on health, quality of life (QoL), and self-esteem.[3,4] Although HO may be present at diagnosis, it is not the most frequent presenting symptom with a prevalence varying between 4 and 15%.[5] After treatment, HO becomes more common, especially in children, with a prevalence up to 55%.[6] Consequences of severe HO include an increased risk of developing metabolic syndrome, cardiovascular disease, respiratory problems, psychosocial complications, and excess mortality.[7-9]

Obesity in patients with CP is ascribed to hypothalamic dysfunction, leading to hyperphagia, decreased resting energy expenditure, insulin resistance, and a distorted day-night rhythm, resulting in daytime somnolence and decreased activity. An additional factor in the development of HO is acquired hypopituitarism, for which adequate timing and dosing of growth hormone, thyroxine, glucocorticoids, and sex steroid treatment is essential.[10,11]

One of the risk factors for HO at follow-up is the degree of hypothalamic involvement at time of diagnosis.[3,12-16] Also, higher preoperative body mass index (BMI)[17], younger age at diagnosis[8,9] and extent of surgery have been observed to play a role in the development of HO.[18,19]

At present, pharmacotherapeutic options for HO are limited. Bariatric surgical procedures, such as Roux-en-Y gastric bypass, may be a promising treatment for HO, but it requires an irreversible surgical procedure that is not preferable in young patients with CP.[20,21] Therefore, prevention of HO is of primary importance. In the literature, partial resection (PR) has been proposed to reduce HO by limiting hypothalamic damage.[18] Risk-based treatment algorithms have been proposed to select subgroups in which PR may be beneficial.[22,23] To provide more data for these treatment algorithms, the aim of this study was to define the influence of gross total resection (GTR) versus PR on the development of HO and morbid HO in a well-defined cohort during a 10-year period. Second, we analyzed the influence of GTR versus PR on event-free survival (EFS) and neuroendocrine sequelae.

Methods

Patients

All children (i.e., age at CP diagnosis ≤ 18.0 years) and adults diagnosed with CP (including one case suspected of CP with the final diagnosis of sellar xanthogranuloma at pathology) in two university medical centers in the Netherlands between January 2002 and May 2012 were evaluated for potential inclusion (n = 41). Of six patients, auxological data could not be retrieved and therefore they were excluded from further analyses.

Ethics

The medical ethical board of the Academic Medical Center considered the retrospective approach of our study to be within the regulations of the Dutch Medical Research Involving Human Subjects Act, with no requirement to retrieve informed consent from patients or parents.

Study information

All charts were reviewed for auxological data (age, gender, height, and weight) and presenting symptoms, including symptoms of hypothalamic damage, endocrine deficits, as well as visual impairment. Information about immediate (cyst) drainage for relief of intracranial pressure, intended and performed surgery (GTR vs. PR vs. biopsy), and the initial surgical approach (transcranial vs. transsphenoidal) were retrieved. Presence of residual disease or recurrence, subsequent surgery, and postoperative radiotherapy (either adjuvant or in case of tumor progression as salvage therapy) were extracted from the medical charts. At last follow-up, the patients were judged as having no evidence of disease or stable disease depending on the presence of residual tumor on last performed postoperative magnetic resonance imaging (MRI) or as disease-related death in case the patient died during follow-up. Data were collected at the time of initial presentation, postoperatively, and at the last follow-up contact.

Evaluation of magnetic resonance images

Preoperative and postoperative magnetic resonance (MR) scans after the initial surgical intervention or in case of recurrence or progression of the disease, also the MR scan after the second surgical intervention, were reviewed independently by two experienced neuroradiologists, who were blinded for the clinical outcome of patients and for each other's scoring results. Both radiologists scored the following items: preoperative presence of hydrocephalus, hypothalamic edema, and the degree of hypothalamic involvement. Hypothalamic involvement was graded according to the Paris grading system:[16] no hypothalamic involvement (grade 0), tumor abutting or displacing the hypothalamus, or pushing against the bottom of the third ventricle (grade 1), and severe hypothalamic involvement or unidentifiable hypothalamus (grade 2). Postoperative hypothalamic damage was graded as no hypothalamic damage (grade 0),

negligible hypothalamic damage or residual tumor displacing the hypothalamus (grade 1), and significant hypothalamic damage in which the floor of the third ventricle is no longer identifiable (grade 2). The grading system for assessment of the hypothalamic involvement of the CP was discussed with each radiologist separately, but was not discussed in advance between the radiologists themselves. Interobserver agreement for hypothalamic involvement, which could be assessed in 32 patients, was 0.27 (Cohen's kappa) for the preoperative assessment. For the postoperative assessment of hypothalamic involvement, performed in 30 available MR scans, the interobserver agreement was 0.36. Because of the low interobserver agreement, the Paris grading was excluded from (multivariable) analysis. The presence of obesity at diagnosis was therefore used as a surrogate marker for preoperative hypothalamic involvement in multivariable analysis. The tumor was measured in three directions: anterior-posterior (a), transverse (b), and craniocaudal (c), and tumor volume was estimated based on the maximal tumor diameters in these three dimensions (a x b x c / 2).

Postoperatively, the degree of resection was graded radiologically as biopsy if <10% was resected, GTR if all visible tumor was resected on postoperative MRI, and all others as PR. Interobserver agreement for the degree of resection was considered as substantial (Cohen's kappa 0.64).[24]

Weight parameters

For pediatric patients, SD scores for BMI were calculated to allow comparison with children of the same age and gender.[25] In pediatric patients, obesity was defined as a BMI > 2 SD above the population reference value. In adult patients, obesity was defined as a BMI > 30 kg/m^2.[26] A subgroup analysis was done for patients with morbid obesity, defined as a BMI > 3 SD for children and >40 kg/m^2 for adults.

Endocrine evaluation

Pre- and postoperative endocrine evaluations were collected, including all endocrine diagnoses as documented by the treating physician, and all endocrine basal and dynamic tests that had been performed. For analysis of the presence of pituitary disorders, the diagnoses were defined as present when stated as such by the treating physician, using the normative values of their own hospital's laboratory. In addition, the use and timing of endocrine replacement treatment were scored. Panhypopituitarism was defined as present when all anterior pituitary deficiencies were diagnosed in one patient (i.e. growth hormone deficiency (GHD), thyroid-stimulating hormone deficiency (TSHD), and adrenocorticotropic hormone deficiency (ACTHD), and late puberty in children or hypogonadism in adults).

Statistical analysis

Statistical analyses were performed using SPSS (version 23.0, Chicago, IL). Significance levels for all analyses were set at $P < 0.05$. Data are presented as median (range) for continuous data or N (proportion in %) for categorical variables. Obesity, morbid obesity, and age (child versus adult) were analyzed as dichotomous variables. Categorical data were compared using the X^2 test or a Fisher's exact test where appropriate. Continuous data were compared using the Mann-Whitney U test. Simple logistic regression analysis was used to explore the association between the initial operation and recurrence or progression of CP. Multiple logistic regression analyses were performed to identify predictors for HO and morbid HO, including the variables we considered most relevant: preoperative age, tumor volume and the presence of obesity, and degree of resection (GTR vs. PR or biopsy). The 3-year EFS was assessed by the Kaplan-Meier method. We evaluated the effects of surgical intervention and timing of radiotherapy in these curves as well. Survival curves were compared using the log rank test. For multivariable logistic regression and Kaplan-Meier analyses, children and adults are analyzed as one cohort to expand possibilities for proper risk factor and survival analyses.

Results

Patients

Thirty-five patients formed the study cohort, consisting of 21 children and 14 adults (Supplemental Figure 1). Patient characteristics are presented in Table 1. Median follow-up time of the study cohort was 35.6 months (4.1-114.7) after diagnosis. At last follow-up, 23 (65.7%) patients had no evidence of disease and 11 (31.4%) patients had stable disease. One adult patient had died from tumor progression.

Patient characteristics

The most common presenting symptoms are summarized in Table 1. Visual impairment was more common in adults ($P = 0.03$), while endocrine deficiencies, especially GHD, were more frequently diagnosed in children ($P = 0.04$). Obesity at diagnosis was present in four patients, of whom two children (5.6 and 14.7 years) and two adults (52.8 and 57.0 years). None of these four obese patients had been diagnosed with an endocrine deficiency at time of CP diagnosis, although both children were suspected for GHD as they showed a decline in height at presentation. Two of the four obese patients had hydrocephalus at diagnosis. In one of the 35 patients, weight parameters could not be retrieved at time of diagnosis. Fifteen (42.9%) patients had been diagnosed with one or more pituitary disorders at diagnosis (Table 1), of whom one had panhypopituitarism.

Table 1. Differences in demographics and clinical characteristics between pediatric and adult craniopharyngioma patients

Characteristic	Children (N = 21)		Adults (N = 14)		*P*-value
	No.	%	No.	%	
Gender					
Male	7	33.3	8	57.1	0.16
Age at diagnosis					
Median (range)	9.7 (4.0-15.1)		42.1 (18.4-68.0)		n.a.
Weight and height parameters at diagnosis [a]					
Median weight (SDS)	-1.1 (-3.7 to 4.0)				n.a.
Median height (SDS)	-1.8 (-3.4 to 1.0)				n.a.
Median BMI (SDS or kg/m^2)	0.5 (-2.7 to 5.2)		25.6 (18.9-39.0)		n.a.
Symptoms at diagnosis					
Visual impairment	12	57.1	13	92.9	0.03*
Headaches	15	71.4	9	64.3	0.72
Weight gain	4	19.0	4	28.6	0.69
Obesity (n=34) [b]	2	10.0	2	14.3	1.00
Endocrine deficiency at diagnosis	12	57.1	3	21.4	0.04*
Growth hormone deficiency	12		0		0.002*
Central hypothyroidism	3		2		1.00
Central hypocortisolism	1		0		1.00
Pubertal delay / hypogonadism	4		1		0.64
Central precocious puberty	0		n.a.		n.a.
Central diabetes insipidus	0		0		n.a.
Preoperative radiological features (n=32)					
Hydrocephalus	7	36.8	3	23.1	0.47
Hypothalamic edema	6	30.0	6	50.0	0.29
Median tumor volume (cm^3) [c]	10.8 (2.0-320.0)		11.1 (1.0-40.0)		0.61
Surgical resection [d]					0.57
Partial resection	7	33.3	6	42.9	
Gross total resection	14	66.7	8	57.1	
Radiotherapy					
Adjuvant after first surgical resection	4	19.0	1	7.1	0.63
At relapse	4	19.0	3	21.4	1.00
Total	8	38.1	4	28.6	0.72

Table 1. Continued

Characteristic	Children (N = 21)		Adults (N = 14)		*P*-value
	No.	%	No.	%	
Recurrence					0.47
Yes	5	23.8	5	35.7	
Endocrine deficiency at last follow-up	19	90.5	13	92.9	1.00
Growth hormone deficiency	18		7		0.06
Central hypothyroidism	18		12		1.00
Central hypocortisolism	16		10		1.00
Pubertal delay / hypogonadism	11		10		0.13
Central precocious puberty	0		n.a.		n.a.
Central diabetes insipidus	17		9		0.68

[a] For pediatric patients, standard deviation scores (SDS) for height, weight and BMI scores were calculated to allow comparison with children of the same age and gender. For adult patients, BMI was calculated as kg/m^2.
[b] In one patient, weight parameters at diagnosis could not be retrieved.
[c] The tumor was measured in three directions: anterior-posterior (a), transverse (b), and craniocaudal (c) and median tumor volume was estimated based on the maximal tumor diameters in these three dimensions (a x b x c / 2).
[d] The surgical resection was graded radiologically as biopsy if <10% was resected, gross total resection if all visible tumor was resected, and all others as partial resection. For this analysis, all biopsies (n=3) were included in the partial resection group.
[*] Significant p-value
Abbreviations: n.a., not applicable

Radiological features

Preoperative imaging, available in 32 patients, showed hypothalamic edema in 12 patients (37.5%) and hydrocephalus in 10 (31.3%). No significant differences in radiological features were found between pediatric and adult patients.

Treatment strategy and outcome

Three patients needed emergency drainage to relieve increased intracranial pressure and in two patients drainage of a cyst was performed prior to surgical resection. Of 32 patients with available data about intended surgery, radical resection was proposed in 28 patients (87.5%), a limited resection in two (6.3%) patients, and biopsy or drainage of cyst in one (3.1%) patient, respectively (Supplemental Figure S1). The surgical approach was transcranial in 28 (80.0%) patients and transsphenoidal in seven (20.0%) patients. There were no differences in outcome regarding HO, or recurrence or progression of residual disease between the patients who underwent transsphenoidal or transcranial surgery ($P = 1.00$ and $P = 0.16$, respectively).

On postoperative MR scans of the initial surgery, the result was GTR in 21 (60.0%) patients, PR in 11 (31.4%) patients, and biopsy in three (8.6%) patients. Five of the 14 patients who underwent PR or biopsy were directly treated with adjuvant radiotherapy (50-54 Gy). One patient, initially treated with PR, had GTR at progression of disease 5 months later. Intended surgery, performed surgery, or surgical approach did not differ significantly between pediatric and adult patients.

Hypothalamic obesity

At the last follow-up contact, HO was present in 19 (54.3%) patients, of whom eight had morbid obesity. In pediatric patients, HO was more common than in adult patients (66.7% vs. 35.7%, respectively), although the difference did not reach statistical significance ($P = 0.07$). Of the 31 patients without HO at diagnosis, three developed HO after PR (two children, one adult) and 13 after GTR (10 children and one adult) at follow-up. Multivariable logistic regression analysis showed that the presence of obesity at the last follow-up contact was significantly related to GTR (odds ratio (OR) 9.19, 95% CI 1.43-59.01, Table 2).

Table 2. Risk factors associated with hypothalamic obesity at last follow-up in multivariable analysis (N = 35)

Covariate	Obesity (N = 19)	Morbid obesity (N = 8)
	OR (95% CI)	OR (95% CI)
Age at diagnosis		
Child	5.41 (0.81-36.31)	1.47 (0.21-10.30)
Obesity at diagnosis		
Yes	1.92 (0.15-24.58)	12.92 (1.05-158.73)*
Tumor volume (cm^3)	1.01 (0.99-1.02)	1.00 (0.98-1.02)
Surgical resection		
Gross total resection	9.19 (1.43-59.01)*	2.00 (0.27-14.75)

* Significant OR
Abbreviations: CI, confidence interval; OR, odds ratio

Morbid obesity

At the last moment of follow-up, morbid HO was present in eight patients, five of whom were children. Three of these eight patients (two children and one adult) were already obese at diagnosis. For the presence of morbid HO at last follow-up, obesity at diagnosis was a significant risk factor in multivariable analyses (OR 12.92, 95% CI 1.05-158.73), but GTR was not (OR 2.00, 95% CI 0.27-14.75, Table 2). Six of the eight patients with morbid HO at last follow-up had undergone a GTR and two patients a PR. One of the patients with PR was already obese at diagnosis. All eight morbid patients developed TSHD, ACTHD and central diabetes insipidus (CDI) postoperatively. Seven patients developed GHD and four hypogonadism.

Recurrence, progression and event-free survival

Ten patients had a recurrence, or progression of residual disease, of whom two after complete resection and eight after PR or biopsy. The median time to recurrence, or growth of residue, was 8.6 months (0.9-33.2) after the initial operation. At recurrence or progression, patients underwent a second surgical resection (n = 5) and/or received radiotherapy (n = 7, 12.5-54 Gy).

PR or biopsy was a significant risk factor for recurrence or progression of the disease (OR 12.7, $P = 0.006$, 95% CI 2.09-76.70). For patients with a GTR, the EFS was 86%, compared to 42% after PR or biopsy (log-rank 9.2, $P = 0.003$) (Figure 1A). Of the patients who received adjuvant radiotherapy after PR or biopsy, none showed progression of the disease, while eight out of nine patients who did not receive adjuvant radiotherapy after PR or biopsy showed progression of disease (log-rank 8.2, $P = 0.004$) (Figure 1B). The EFS after GTR was similar to that after PR with adjuvant radiotherapy (log-rank 0.6, $P = 0.43$). Radiotherapy, either adjuvant or as salvage therapy, did not influence the presence of HO at follow-up ($P = 0.28$, $P = 0.64$ and $P = 0.68$ respectively), nor did the development of recurrence, or progression of residual disease, at follow-up ($P = 0.45$).

Endocrine outcome

At the last follow-up contact, 32 (91.4%) patients had a pituitary disorder, of whom 15 (42.9%) patients had panhypopituitarism (Table 3).

Of the 25 patients with GHD at follow-up, 13 were diagnosed after surgical resection. Growth hormone (GH) treatment was started in 23 patients, after a median of 0.9 year (range 0.3-3.9) after initial surgery. The time interval between the surgical resection and start of GH treatment, did not differ significantly between children and adults ($P = 0.05$), obese and nonobese patients at last follow-up ($P = 0.55$), patients with PR versus GTR ($P = 0.84$), or between patients who had recurrence or progression of residual disease at follow-up ($P = 0.74$). The presence of GHD did not influence the development of HO at follow-up ($P = 0.14$).

Of the 30 patients with TSHD at follow-up, five had been diagnosed at CP diagnosis, 23 directly postoperatively, and two during follow-up (0.6 and 1.1 years after initial surgical resection, respectively).

Of the 26 patients in whom ACTHD was diagnosed, 23 were diagnosed directly postoperatively, of whom eight were dynamically tested. Of the other three patients, one patient had been diagnosed with ACTHD at diagnosis, and two were diagnosed during follow-up. ACTHD was more frequently present in obese versus nonobese patients; however, this difference was not significant ($P = 0.05$).

Of the 21 patients who developed hypogonadism, five had been diagnosed prior to diagnosis and 16 were diagnosed during follow-up.

CDI developed in 26 patients after the surgical resection, of whom six patients underwent PR and 20 GTR. At last follow-up, 15 patients had panhypopituitarism. Both CDI and panhypopituitarism were more frequently seen in patients who underwent GTR compared to PR (n = 20 and n = 13, respectively; $P = 0.01$). Panhypopituitarism was not related to the presence of HO at follow-up ($P = 0.05$). Radiotherapy, either adjuvant or as salvage therapy, did not influence the presence of panhypopituitarism at follow-up ($P = 0.12$, $P = 1.00$, and $P = 0.20$ respectively).

Figures 1A and 1B. Recurrence-free proportion of patients who underwent a gross total resection (GTR) versus partial resection (PR) or biopsy (A) and of patients who received adjuvant radiotherapy (RT) after partial resection or biopsy versus no adjuvant RT (B).

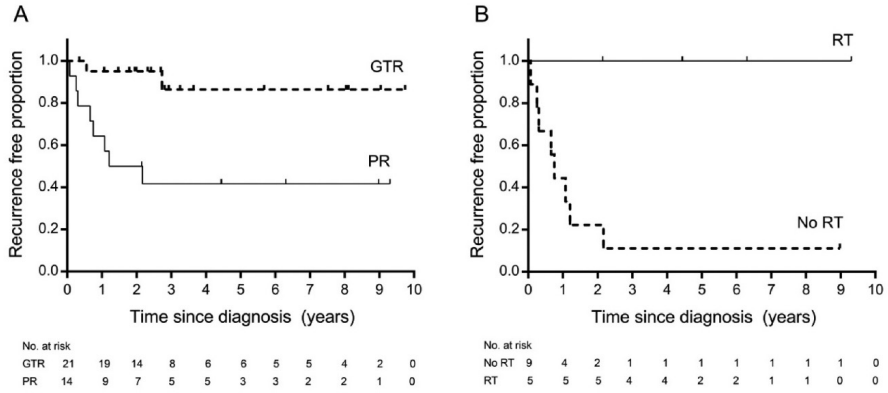


Table 3. Differences in demographics and clinical characteristics between 35 craniopharyngioma patients with and without obesity at follow-up

Characteristic	Obesity at follow-up (N = 19)		No obesity at follow-up (N = 16)		*P*-value
	No.		No.	%	
Gender					0.92
Male	8	42.1	7	43.8	
Age at diagnosis					0.07
Child	14	73.7	7	43.8	
Adult	5	26.3	9	56.3	
Symptoms at diagnosis					
Visual impairment	12	63.2	13	81.3	0.29
Headaches	13	68.4	11	68.8	0.98
Weight gain	7	36.8	1	6.3	0.05

Table 3. Continued

Characteristic	Obesity at follow-up (N = 19)		No obesity at follow-up (N = 16)		*P*-value
Obesity (n=34) [a]	3	15.8	1	6.7	0.61
Endocrine deficiency at diagnosis	8	42.1	7	43.8	0.92
Growth hormone deficiency	7		5		0.95
Central hypothyroidism	1		4		0.15
Central hypocortisolism	0		1		0.42
Pubertal delay / hypogonadism	3		2		1.00
Central precocious puberty	0		0		n.a.
Central diabetes insipidus	0		0		n.a.
Preoperative radiological features (n=32)					
Hydrocephalus	6	33.3	4	28.6	1.00
Hypothalamic edema	9	47.4	3	23.1	0.27
Median tumor volume (cm^3) [b]	12.4 (5-320)		9.2 (1-192)		0.15
Intended surgical resection					0.32
Complete resection	16	84.2	12	75.0	
Limited resection	1	5.3	3	18.8	
Unknown	2	10.5	1	6.3	
Surgical resection [c]					0.03*
Partial resection	4	21.1	9	56.3	
Gross total resection	15	78.9	7	43.8	
Radiotherapy					
Adjuvant after first surgical resection	2	10.5	3	18.8	0.64
At relapse	3	15.8	4	25.0	0.68
Total	5	26.3	7	43.8	0.28
Recurrence					0.45
Yes	4	21.1	6	37.5	
Endocrine deficiency at last follow-up	18	94.7	14	87.5	0.58
Growth hormone deficiency	16		9		0.14
Central hypothyroidism	18		12		0.16
Central hypocortisolism	17		9		0.05
Pubertal delay / hypogonadism	11		10		0.74
Central precocious puberty	0		0		n.a.
Central diabetes insipidus	17		9		0.10
Panhypopituitarism	11		4		0.05

* Significant *P*-value

[a] In one patient, weight parameters at diagnosis could not be retrieved

[b] The tumor was measured in three directions: anterior-posterior (a), transverse (b), and craniocaudal (c) and median tumor volume was estimated based on the maximal tumor diameters in these three dimensions (a x b x c / 2)
[c] The surgical resection was graded radiologically as biopsy if <10% was resected, gross total resection if all visible tumor was resected and all others as partial resection. For this analysis, all biopsies (n=3) were included in the partial resection group.
Abbreviations: n.a., not applicable

Discussion

In this well-defined cohort of 35 patients with CP, we confirm that HO is less frequent after PR than after GTR. However, PR does not seem to prevent morbid obesity in all, especially not in patients with obesity at diagnosis. These results point to the existence of a preoperative hypothalamic disorder, which can only partially be influenced by the degree of resection. However, as PR seems to reduce the occurrence of panhypopituitarism and CDI, it still seems beneficial to aim for PR, even when obesity is present at diagnosis. After PR, reduced EFS is seen when compared to GTR, which seems to be overcome with adjuvant radiotherapy. The possible late adverse effects of radiotherapy, not studied in this cohort, must however be taken into account. All these factors should be considered when developing a treatment algorithm for these patients.

Recent studies suggest that it seems reasonable to aim for hypothalamus-sparing surgery, especially in patients with substantial hypothalamic involvement prior to surgery.[18,27] For this reason, we evaluated the influence of preoperative hypothalamic involvement and the extent of surgical resection on the development of HO. Of the different tools developed to assess hypothalamic involvement, the Paris grading is a widely used scoring system.[28] Therefore, we also intended to use the Paris grading in our cohort to define the existence of preoperative hypothalamic involvement. However, because of a low interobserver agreement for preoperative hypothalamic involvement between two well-experienced neuroradiologists, we instead used obesity at diagnosis as surrogate marker of possible preoperative hypothalamic involvement. For future studies, alternative MRI criteria to define hypothalamic involvement, such as tumor extension toward the mammillary bodies, should be considered, and the interobserver variability of scoring systems deserves further attention.[28,29]

For HO in general, GTR is a risk factor, indicating PR may be preferential. The benefit of reducing HO versus the increased recurrence rate after hypothalamus-sparing surgery, however, is still an important issue of debate.[18,30] In our cohort, PR shows a higher recurrence rate, which, when evaluated in more detail, was only seen in the patients who did not receive adjuvant radiotherapy after initial surgery. This might implicate that radiotherapy is favorable after PR; however, we did not study possible negative late effects of adjuvant radiotherapy, such as neurocognitive impairment and the development of meningioma.[31] The role and timing of radiotherapy after PR must be studied in future prospective trials, taking into account the option of direct (stereotactic)

radiotherapy after initial surgery, or an initial wait-and-scan policy following initial surgery with adjuvant radiotherapy in case of progression.[32] This last option seems to be most favorable, especially in young children. Also, advancements in the field of radiotherapy, such as proton beam therapy, may reduce radiation exposure to healthy tissues, and possibly diminish the occurrence of adverse effects in future CP patients.[33]

Neuroendocrine sequelae are frequently observed in CP patients, either as presenting symptom or as postoperative complication. In our study, postoperative panhypopituitarism was mainly seen in patients who underwent GTR. Recently, in accordance with our findings, it has been demonstrated that conservative surgery may limit neuroendocrine sequelae.[34] The relation between endocrine deficiencies and the development of obesity in childhood cancer survivors has been previously observed. In our cohort, the majority of patients with ACTH deficiency had HO at follow-up, either reflecting the degree of hypothalamic damage or possibly reflecting too high doses of hydrocortisone substitution therapy. Next to high doses of hydrocortisone, suboptimal GH and thyroid hormone replacement therapy may influence BMI. Adequate screening and timely treatment of endocrinopathies might favor the metabolic state, and possibly diminish the degree of obesity. Dynamic testing, especially in case of suspicion of ACTHD, should be considered to reduce overtreatment with steroids.

Several limitations of the study should be noted. First, as this was a retrospective cohort analysis, differences in follow-up time of the individual CP patients were present. This may have possibly influenced the prevalence of endocrine disorders, obesity, and EFS in the patients with the shortest follow-up time. Moreover, due to the retrospective study design, we could not reliably evaluate neuropsychological outcome or quality of survival at follow-up. Second, the cohort was limited due to the rarity of the disease. This is reflected in the sometimes wide confidence intervals of the risk factor analyses. Third, we included both adult and pediatric patients. As histologic subtypes and disease processes differ among different ages, the mix of both age groups made the cohort more heterogeneous. Finally, we used obesity at diagnosis as surrogate marker for hypothalamic involvement, instead of the "gold standard" that is grading on MRI. This was chosen, because the interobserver agreement of both pre- and postoperative hypothalamic involvement based on neuroimaging was too low, making these results unreliable.

Despite these limitations, the results presented here represent outcomes of a well-defined cohort of CP patients, including all auxological and treatment data, MR images, and endocrine data (laboratory measurements, stimulation tests, as well as timing of hormonal treatment). The fact that both adults and children were included in this cohort has empowered the statistical analyses. National registry databases and international collaborations should be encouraged, as these will increase patient numbers and optimize future retrospective and prospective cohort studies.[35]

From this cohort of CP patients with well-documented follow-up data, it seems that the presence of obesity at diagnosis as well as extent of surgical resection, are both related to the development of (morbid) HO later in life. The observation that the development of morbid obesity is strongly related to the presence of obesity at diagnosis indicates preoperative hypothalamic involvement that may not be overcome by limiting the degree of surgical resection. However, as GTR increases the risk of neuroendocrine sequelae at follow-up, aiming for a PR will still be beneficial, even in the obese. Considering all these factors, preoperative risk-based treatment algorithms must be developed, weighing the risk of developing HO in relation to the presence of obesity at diagnosis, the degree of resection, the risk of recurrence, the risk of adverse effects due to adjuvant radiotherapy taking into account the age of the patient, and the development of neuroendocrine sequelae. To prevent morbid HO, patients (and their parents) should be actively counseled preoperatively by the multidisciplinary team about potential change in eating behavior, a reduced metabolic state, and the limited pharmacotherapeutic options for HO. Postoperatively, early involvement of a dietician, psychologist, and physiotherapist may prevent development or further aggravation of HO by providing individual lifestyle and dietary advice, although this can be very challenging in some cases. Regular visits to the outpatient clinic should be offered to closely monitor weight development and to support patients. As HO has a major impact on the QoL in these patients, pre- and postoperative management should be individualized and regularly discussed within the multidisciplinary team.

References

1. Bunin GR, Surawicz TS, Witman PA, Preston-Martin S, Davis F, Bruner JM. The descriptive epidemiology of craniopharyngioma. *Journal of neurosurgery.* 1998;89(4):547-551.
2. Zacharia BE, Bruce SS, Goldstein H, Malone HR, Neugut AI, Bruce JN. Incidence, treatment and survival of patients with craniopharyngioma in the surveillance, epidemiology and end results program. *Neuro-oncology.* 2012;14(8):1070-1078.
3. Muller HL, Gebhardt U, Teske C, et al. Post-operative hypothalamic lesions and obesity in childhood craniopharyngioma: results of the multinational prospective trial KRANIOPHARYNGEOM 2000 after 3-year follow-up. *Eur J Endocrinol.* 2011;165(1):17-24.
4. Sterkenburg AS, Hoffmann A, Gebhardt U, Warmuth-Metz M, Daubenbuchel AM, Muller HL. Survival, hypothalamic obesity, and neuropsychological/psychosocial status after childhood-onset craniopharyngioma: newly reported long-term outcomes. *Neuro-oncology.* 2015;17(7):1029-1038.
5. Karavitaki N, Cudlip S, Adams CB, Wass JA. Craniopharyngiomas. *Endocr Rev.* 2006;27(4):371-397.
6. Cohen M, Guger S, Hamilton J. Long term sequelae of pediatric craniopharyngioma - literature review and 20 years of experience. *Front Endocrinol (Lausanne).* 2011;2:81.
7. Muller HL. Consequences of craniopharyngioma surgery in children. *The Journal of clinical endocrinology and metabolism.* 2011;96(7):1981-1991.
8. Lustig RH, Post SR, Srivannaboon K, et al. Risk factors for the development of obesity in children surviving brain tumors. *J Clin Endocrinol Metab.* 2003;88(2):611-616.
9. Haliloglu B, Atay Z, Guran T, et al. Risk factors for mortality caused by hypothalamic obesity in children with hypothalamic tumours. *Pediatr Obes.* 2016;11(5):383-388.
10. Geffner M, Lundberg M, Koltowska-Haggstrom M, et al. Changes in height, weight, and body mass index in children with craniopharyngioma after three years of growth hormone therapy: analysis of KIGS (Pfizer International Growth Database). *The Journal of clinical endocrinology and metabolism.* 2004;89(11):5435-5440.
11. Erfurth EM. Endocrine aspects and sequel in patients with craniopharyngioma. *Journal of pediatric endocrinology & metabolism : JPEM.* 2015;28(1-2):19-26.
12. Muller HL, Emser A, Faldum A, et al. Longitudinal study on growth and body mass index before and after diagnosis of childhood craniopharyngioma. *J Clin Endocrinol Metab.* 2004;89(7):3298-3305.
13. Muller HL, Bueb K, Bartels U, et al. Obesity after childhood craniopharyngioma--German multicenter study on pre-operative risk factors and quality of life. *Klin Padiatr.* 2001;213(4):244-249.
14. Meuric S, Brauner R, Trivin C, Souberbielle JC, Zerah M, Sainte-Rose C. Influence of tumor location on the presentation and evolution of craniopharyngiomas. *J. Neurosurg.* 2005;103(5 Suppl):421-426.
15. Van Gompel JJ, Nippoldt TB, Higgins DM, Meyer FB. Magnetic resonance imaging-graded hypothalamic compression in surgically treated adult craniopharyngiomas determining postoperative obesity. *Neurosurgical focus.* 2010;28(4):E3.
16. Puget S, Garnett M, Wray A, et al. Pediatric craniopharyngiomas: classification and treatment according to the degree of hypothalamic involvement. *Journal of neurosurgery.* 2007;106(1 Suppl):3-12.
17. Vinchon M, Weill J, Delestret I, Dhellemmes P. Craniopharyngioma and hypothalamic obesity in children. *Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery.* 2009;25(3):347-352.
18. Elowe-Gruau E, Beltrand J, Brauner R, et al. Childhood craniopharyngioma: hypothalamus-sparing surgery decreases the risk of obesity. *J Clin Endocrinol Metab.* 2013;98(6):2376-2382.
19. Gleeson H, Amin R, Maghnie M. 'Do no harm': management of craniopharyngioma. *European Journal of Endocrinology.* 2008;159:S95-S99.

20. Wijnen M, Olsson DS, van den Heuvel-Eibrink MM, et al. Efficacy and safety of bariatric surgery for craniopharyngioma-related hypothalamic obesity: a matched case-control study with 2 years of follow-up. *Int J Obes (Lond).* 2017;41(2):210-216.

21. Bretault M, Boillot A, Muzard L, et al. Clinical review: Bariatric surgery following treatment for craniopharyngioma: a systematic review and individual-level data meta-analysis. *J Clin Endocrinol Metab.* 2013;98(6):2239-2246.

22. Muller HL, Albanese A, Calaminus G, et al. Consensus and perspectives on treatment strategies in childhood craniopharyngioma: results of a meeting of the Craniopharyngioma Study Group (SIOP), Genova, 2004. *Journal of pediatric endocrinology & metabolism : JPEM.* 2006;19 Suppl 1:453-454.

23. The United Kingdom Children's Cancer Study Group and British Society of Paediatric Endocrinology & Diabetes. Craniopharyngioma. In: Spoudeas HA. Paediatric endocrine tumours. A multi-disciplinary consensus statement of best practice from a working group convened under the auspices of the BSPED and UKCCSG (rare tumour working groups). BSPED and UKCCSG, UK; 2005. (https://www.bsped.org.uk/clinical/docs/RareEndocrineTumour_final.pdf) [Accessed June 16, 2017].

24. Viera AJ, Garrett JM. Understanding interobserver agreement: the kappa statistic. *Fam Med.* 2005;37(5):360-363.

25. Fredriks AM, van Buuren S, Wit JM, Verloove-Vanhorick SP. Body index measurements in 1996-7 compared with 1980. *Archives of disease in childhood.* 2000;82(2):107-112.

26. World Health Organization (WHO). Factsheet; Obesity and Overweight. World Health Organization, 2016. (http://www.who.int/mediacentre/factsheets/fs311/en/) [Accessed June 14, 2017].

27. Hoffmann A, Warmth-Metz M, Gebhardt U, et al. Childhood craniopharyngioma - changes of treatment strategies in the trials KRANIOPHARYNGEOM 2000/2007. *Klinische Padiatrie.* 2014;226(3):161-168.

28. Muller HL. Preoperative staging in childhood craniopharyngioma: standardization as a first step towards improved outcome. *Endocrine.* 2016;51(1):1-3.

29. Roth CL, Eslamy H, Werny D, et al. Semiquantitative analysis of hypothalamic damage on MRI predicts risk for hypothalamic obesity. *Obesity (Silver Spring).* 2015;23(6):1226-1233.

30. Elliott RE, Hsieh K, Hochm T, Belitskaya-Levy I, Wisoff J, Wisoff JH. Efficacy and safety of radical resection of primary and recurrent craniopharyngiomas in 86 children. *Journal of neurosurgery. Pediatrics.* 2010;5(1):30-48.

31. Kiehna EN, Merchant TE. Radiation therapy for pediatric craniopharyngioma. *Neurosurgical focus.* 2010;28(4):E10.

32. Clinical trials (US). Prospective Study of Children and Adolescents With Craniopharyngioma. National Institutes of Health, US, 2016 (https://clinicaltrials.gov/ct2/show/NCT01272622) [Accessed December 12, 2016].

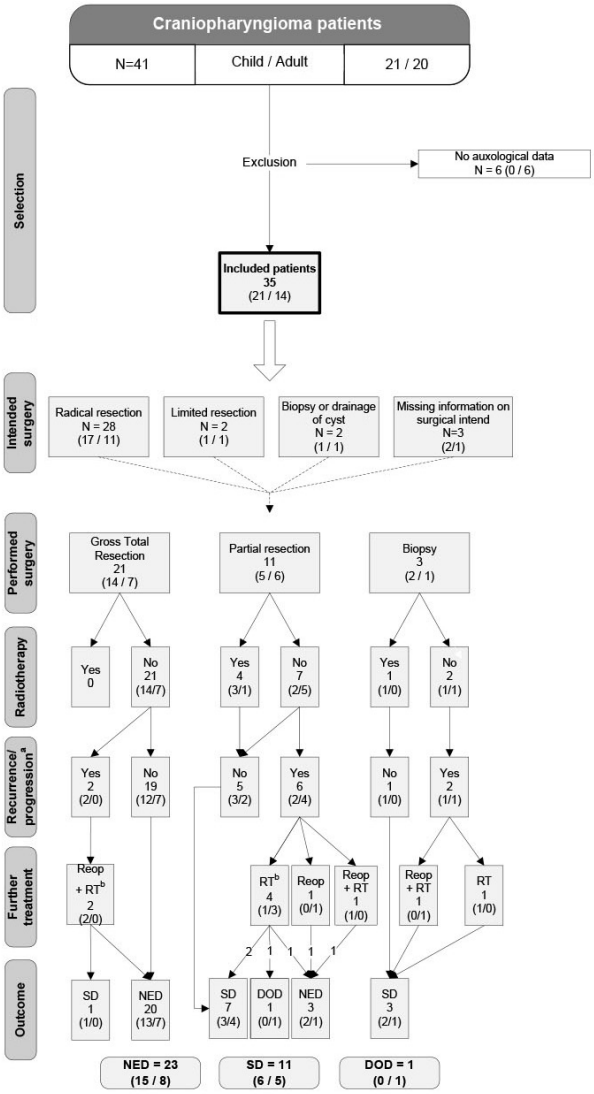
33. Beltran C, Roca M, Merchant TE. On the benefits and risks of proton therapy in pediatric craniopharyngioma. *Int J Radiat Oncol Biol Phys.* 2012;82(2):e281-287.

34. Tan TS, Patel L, Gopal-Kothandapani JS, et al. The neuroendocrine sequelae of paediatric craniopharyngioma: a 40-year meta-data analysis of 185 cases from three UK centres. *European journal of endocrinology.* 2017;176(3):359-369.

35. Bakhsheshian J, Jin DL, Chang KE, et al. Risk factors associated with the surgical management of craniopharyngiomas in pediatric patients: analysis of 1961 patients from a national registry database. *Neurosurgical focus.* 2016;41(6):E8.

Supplementary material

Supplemental Figure 1. Flow chart of patient selection and treatment characteristics



[a] Recurrence after complete resection (n=2) or progression of residual disease (n=8)
[b] For two patients, radiotherapy was planned but not yet performed
Abbreviations: DOD: death of disease; N: Number of patients (child/adult); NED: no evidence of disease; Reop: Reoperation; RT: radiotherapy; SD: stable disease

3

Pathophysiology and individualized treatment of hypothalamic obesity following craniopharyngioma and other suprasellar tumors: a systematic review

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Abstract

The development of hypothalamic obesity (HO) following craniopharyngioma (CP) and other suprasellar tumors leads to reduced patient quality of life. No treatment algorithms are currently available for management of HO. Depending on which hypothalamic nuclei are destroyed, the pathophysiologic mechanisms and clinical symptoms that contribute to HO differ among patients. Herein, we review the contribution of the hypothalamus to the pathophysiologic mechanisms and symptoms underlying CP-associated HO. Additionally, we performed a systematic search of MEDLINE and Embase to identify all intervention studies for weight management in patients with CP or other suprasellar tumors published until September 2017. The search yielded 1866 publications, of which 40 were included. Of these 40 studies, we identified four modalities for intervention (i.e., lifestyle, dietary, pharmacotherapeutic, or surgical) within six clinical domains (i.e., psychosocial disorders, hyperphagia, sleep disturbances, decreased energy expenditure, hyperinsulinemia, and hypopituitarism). We used the findings from our systematic review, in addition to current knowledge on the pathophysiology of HO, to develop an evidence-based treatment algorithm for patients with HO caused by CP or other suprasellar tumors. Although the individual effects of the HO interventions were modest, beneficial individual effects may be achieved when the pathophysiologic background and correct clinical domain are considered. These two aspects can be combined in an individualized treatment algorithm with a stepwise approach for each clinical domain. Recently elucidated targets for HO intervention were also explored to improve future management of HO for patients with CP and other suprasellar tumors.

Essential points

- Feeding behavior is characterized by three processes, that is, meal initiation, meal termination and food choice, and is controlled by different interconnected parts of the brain that integrate central and peripheral signals to determine the status of the energy balance
- Hypothalamic obesity in patients with craniopharyngioma is caused by an increase in energy intake, a decrease in sympathetic activity and an increase in parasympathetic activity
- Damage to the mediobasal hypothalamus causes dysfunction of proopiomelanocortin and agouti-related peptide-neuropeptide Y neurons, disrupts integration of central and peripheral hormones, and results in inappropriate food intake
- A decrease in sympathetic activity lowers total energy expenditure, whereas increased parasympathetic activity may cause hyperinsulinemia and fat accumulation
- Damage to hypothalamic nuclei and surrounding structures causes clinical symptoms that may contribute to the development of hypothalamic obesity and can be divided into six domains: psychosocial disorders, hyperphagia, sleep disturbances, decreased energy expenditure, hyperinsulinemia, and hypopituitarism
- Using six clinical domains as a starting point for an individual treatment algorithm, lifestyle, dietary, pharmacotherapeutic, or surgical interventions may be successful in individual patients with craniopharyngioma to target hypothalamic obesity
- New interventions targeting the hypothalamus (if partially damaged) or other receptors in the brain and/or periphery (if the hypothalamus is completely damaged) are required to improve future hypothalamic obesity management in patients with craniopharyngioma

Introduction

Craniopharyngioma (CP) is a rare embryonic brain tumor of the sellar and parasellar region.[1] It is histologically benign (World Health Organization grade I), with the adamantinomatous subtype occurring more frequently in younger patients (10 to 14 years of age) and the papillary subtype occurring more frequently in adult and elderly patients (>50 years of age).[2] Despite its benign histologic characteristics and high survival rates (20-year survival of 88%), CP may cause severe morbidity from invasion into adjacent tissues and structures.[3] This can result in damage to the optic nerve, pituitary gland, or hypothalamus, resulting in visual impairment, pituitary dysfunction, and disturbances in sleep, temperature regulation, thirst sensation, and eating behaviors.[4]

Hypothalamic obesity (HO) is one of the most severe sequelae in patients with CP, but it may also occur in patients with other tumors and lesions in the hypothalamic region, such as germinoma or astrocytoma. HO not only reduces patient quality of life (QoL) but also increases risk of metabolic disease, resulting in excess morbidity and mortality.[5-7] Although HO may be present at diagnosis, weight gain occurs primarily during the first 6 to 12 months after initial surgical treatment.[8,9] Hypothalamic radiation exposure is also a reported risk factor for HO.[10] Postoperatively, patients may experience increases in body weight up to 55%, but a plateau in weight gain is observed after long-term follow-up.[3,11]

HO is predominantly caused by damage to the ventromedial hypothalamus (VMH) and arcuate nucleus, which regulate hunger, satiety, and energy balance.[12,13] Peripheral satiety and hunger hormones, such as insulin, ghrelin, and leptin, play an essential role in the regulation of energy balance and signaling to the VMH and arcuate nucleus. Damage to the VMH or arcuate nucleus prevents proper integration of peripheral hormones and promotes excessive caloric intake and decreased caloric expenditure. This can result in extreme and progressive weight gain.

Because the QoL of CP and other suprasellar tumor survivors is greatly determined by the severity of obesity, HO interventions are urgently needed.[3] Hypothalamic damage may be minimized by limiting surgical interventions and using new radiotherapy techniques, such as proton beam therapy.[14,15] Additionally, molecular-targeted therapies may soon become available for certain genetic variants of CP.[16-19] However, improving treatment will not prevent HO in all patients, particularly not for those in whom hypothalamic damage has already occurred.

Several nonsystematic reviews have summarized intervention studies for HO.[20-22] Two recently published systematic reviews focused on interventions for weight management for pediatric survivors of brain tumors, in general.[23,24] All of these reviews concluded that no overall effective treatment strategies are currently available for HO. However, we hypothesize that some weight interventions may be beneficial for some selected patients, if these interventions target the

underlying pathophysiologic causes of HO. Moreover, by understanding the pathophysiologic mechanisms that contribute to HO, targets for new potential interventions may be identified. Therefore, we reviewed the pathophysiologic mechanisms contributing to HO in patients with CP or other suprasellar tumors and identified targets for HO interventions. We also conducted a systematic review of all interventions for HO in patients with CP and other suprasellar tumors and combined current knowledge of the pathophysiologic mechanisms of HO with our systematic review findings to generate an individualized treatment algorithm for patients with CP- and other suprasellar tumor–mediated HO.

Pathophysiology of hypothalamic obesity

Neuroendocrine regulation of energy intake

Neural circuitry of feeding behavior

During the last few decades, both basic and clinical research studies have improved our knowledge about the neural circuits that control feelings of hunger and satiety. In general, three processes characterize feeding behavior: meal initiation, meal termination, and food choice. These three processes are all driven by specific central and peripheral signals and are regulated at different, but highly connected, neural circuits in the brain.[25]

Meal initiation is driven by a negative energy balance and by cues that predict the reward of food (*i.e.*, its palatability). In general, highly palatable foods contain considerable amounts of sugar and fat, making them calorie-dense foods. Meal initiation is primarily regulated by the hypothalamus and is a major process highly likely to be disturbed in patients with CP.[26] Destruction of the VMH, which often extends to the arcuate nucleus, increases feeding behavior and results in obesity.[27] Other nuclei, such as the paraventricular nucleus (PVN) and lateral hypothalamic area (LHA), also play a role in hyperphagia and obesity.[28] The single-minded homolog 1 (SIM1) transcription factor is important for development of the PVN, and *SIM1* haploinsufficiency results in hyperphagia and obesity, perhaps by reducing oxytocin signaling.[29] In Prader-Willi syndrome, the development of HO involves *SIM1* deficiency and reduced oxytocin signaling in the PVN.[30,31] The LHA contains two sets of orexigenic neurons that express either orexin or melanin-concentrating hormone (MCH). Orexin-expressing neurons become rapidly activated after a period of fasting and innervate many hypothalamic neurons that increase motivation to consume palatable foods.[32] MCH-expressing neurons demonstrate similar orexigenic effects, with upregulation of MCH target genes within 24 hours after food deprivation.[33] Furthermore, MCH-expressing neurons respond to elevated glucose levels after caloric food intake, promoting prolonged food consumption and overeating.[34]

Termination of meals involves the response to gut-derived hormones, such as cholecystokinin (CCK), peptide YY (PYY), or glucagon-like peptide 1 (GLP-1), which are released upon entrance of nutrients in the gut and enhanced by signals originating from gastric stretch.[35] Some signals, such as CCK, peak at the end of meals and activate the afferent vagus nerve, which projects to the nucleus tractus solitarii in the brainstem.[36] Cells of the nucleus tractus solitarii forward this information to many regions in the brain, including the lateral parabrachial nucleus, the hypothalamus, and the basal forebrain. Rostral brain regions, particularly the hypothalamus, can overrule satiation, allowing animals to increase meal size when in a food-deprived, negative energy balance state. Food-restricted rats with lesions between the brainstem and midbrain do not increase their meal sizes in response to their negative energy balances.[37] This supports that neural circuits in the brainstem are involved in satiation (*i.e.*, limiting meal size) and that the effect of hunger on increasing meal size is signaled to the brainstem by rostral brain regions. Indeed, oxytocinergic paraventricular neurons from the hypothalamus directly increase the sensitivity of brainstem nuclei, activated by CCK, to increase satiation.[38] Because satiation is primarily regulated at the brainstem, patients with CP less likely experience difficulties in meal termination, although indirect effects, in which a hunger signal projects from the damaged hypothalamus to the brainstem to increase meal size, cannot be excluded.

Food choice is influenced by learned associations between food cues (*e.g.*, sight and smell) and postingestive experiences (*i.e.*, taste and nutrient sensing) and involves the mesolimbic reward system and decision-making neural circuitry, such as those of the prefrontal cortex and amygdala.[39] Food rewards elevate dopamine concentrations and activate the nucleus accumbens in rodents and humans.[40] The individual response to food rewards differs greatly; for example, drivers for palatable food are moderated by cognition, specifically executive functions. These higher brain functions support self-regulation of eating behavior and map to networks that include lateral and dorsomedial regions of the brain, such as the dorsolateral prefrontal cortex, the dorsal anterior cingulate, and the parietal cortex.[39] Easy access to food in current Western cultures challenges the internal goal of staying healthy (*i.e.*, maintaining an optimal weight) vs consuming food that is rewarding and directly available. Balancing between cognition (*e.g.*, "I should not eat more") and reward (*e.g.*, "I like that pie") is an important determinant of current ingestive behavior in humans. In patients with CP, specific behavioral changes and neurocognitive impairment are frequently present, such as impulse-control disorders that result in aggressiveness and episodic rage when food or other rewarding products are restricted. Hypothalamic damage caused by CP or other suprasellar tumors may produce inappropriate feelings of starvation or disturbed neuropsychologic behaviors that result in excessive food intake.

In summary, the three processes involved in food intake involve different, but highly connected, locations in the brain: meal initiation in the hypothalamus, meal termination in the hindbrain, and meal choice in higher brain areas. Hypothalamic damage may particularly disturb meal initiation, although other processes can also be affected because of afferent and efferent hypothalamic projections throughout the brain.

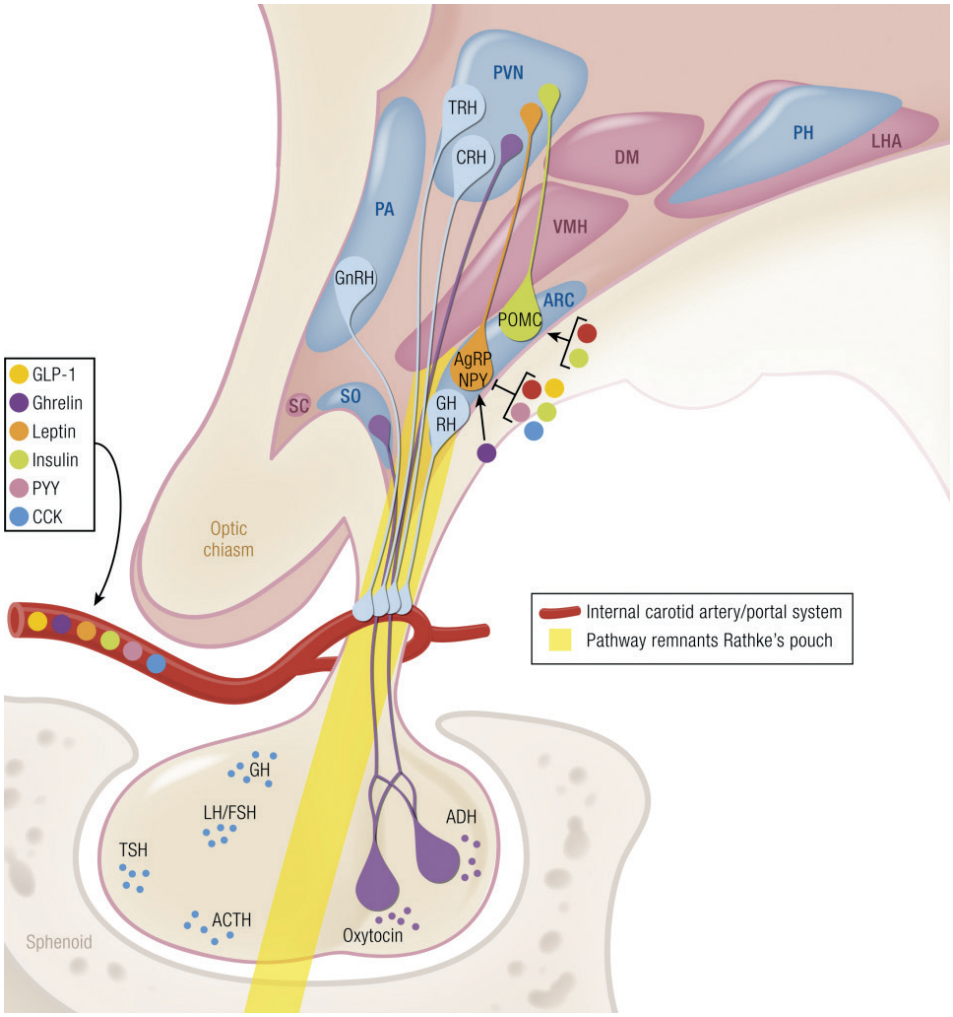
Hypothalamic regulation of energy intake

The hypothalamus is the key regulator of energy homeostasis, as it adjusts both energy intake and expenditure. Hypothalamic-driven energy intake mainly compels the process of meal initiation. The hypothalamus senses a variety of gut- and fat-derived hormones that inform the brain about the body's energy balance status. The hypothalamus contains neural populations in the arcuate nucleus with established roles in the regulation of energy balance: proopiomelanocortin (POMC) and agouti-related peptide (AgRP)/neuropeptide Y (NPY) neurons (Figure 1). These neurons express orexigenic (*e.g.*, NPY) and anorexigenic neuropeptides, such as α-melanocyte-stimulating hormone (α-MSH), that are released or inhibited when peripheral signals, such as PYY, GLP-1, ghrelin, leptin, or insulin, reach the hypothalamus.[41]

AgRP-expressing neurons exhibit orexigenic effects when activated by hunger hormones such as ghrelin.[42] In contrast, satiety hormones, such as PYY, GLP-1, leptin, insulin, and CCK, inhibit the activity of AgRP-expressing neurons. AgRP-expressing neurons are highly active after a period of starvation, leading to increased food intake. Optogenetic and chemogenetic activation of AgRP-expressing neurons strongly stimulates the search for food and initiation of food intake.[43,44] Damage to these neurons may result in loss of appetite, with extreme starvation and cachexia. Clinically, this phenomenon, also known as diencephalic syndrome, is an atypical presenting symptom of CP.[45] Conversely, activation of AgRP-expressing neurons in animals stimulates food-seeking behavior, even when obesity is present. From an evolutionary standpoint, ensuring sufficient energy intake is a behavior required for survival, whereas overconsumption requires a longer time to affect health and therefore minimally influences natural selection.[46] The brain has redundant systems to ensure energy intake, but the capacity to protect against overeating is limited. This may explain why damage to hypothalamic circuits is more likely to result in obesity than in cachexia.

POMC-expressing neurons are activated by leptin and insulin and propagate an anorexigenic response farther into the brain via MSH. These neurons project to and activate, among others, neurons in the PVN.[47] Loss of the *POMC* gene or the melanocortin 4 receptor (*MC4R*) gene (*i.e.*, a brain receptor for POMC-derived melanocortins) results in obesity in mice and humans.[48,49] When the medial hypothalamic nuclei or PVN are damaged, the neurons expressing these anorexigenic neuropeptides (*e.g.*, MSH and oxytocin) are destroyed. This may explain why an increased drive to eat frequently underlies obesity. In summary, POMC-expressing neurons are located in the

Figure 1. Schematic overview of the human hypothalamus



CPs most likely arise from epithelial remnants of the craniopharyngeal duct or the Rathke pouch (light yellow bar). Remnants of the Rathke pouch may be located in infrasellar, sellar, or suprasellar regions and may give rise to a CP in these locations. Purely sellar or infrasellar CP is very rare. CP expansion frequently occurs, with destruction of the optic chiasm or midbrain, resulting in obstructive hydrocephalus. The hypothalamus consists of many hypothalamic nuclei, which are all highly connected through neural pathways. The connection between the arcuate nucleus and paraventricular nucleus is emphasized. Afferent and efferent blood vessels provide a pipeline for pituitary hormones, as well as hunger and satiety hormones that stimulate hypothalamic neuron orexigenic and anorexigenic responses, respectively. ARC, arcuate nucleus; CRH, corticotropin-releasing hormone; DM, dorsomedial hypothalamic nucleus; OC, optic chiasm; PA, preoptic area; PH, posterior hypothalamic nucleus; SC, suprachiasmatic nucleus; SO, supraoptic nucleus; VMH, ventromedial hypothalamus.

hypothalamic arcuate nucleus. AgRP-expressing neurons are activated by peripherally-derived hunger hormones and propagate feeding behavior. In contrast, satiety hormones stimulate POMC neurons to decrease appetite. In HO satiety signals fail to activate neurons such as those expressing POMC that propagate the satiety signal farther into the brain and finally to the brainstem.

Neuroendocrine regulation of energy expenditure

Role of the hypothalamus in sympathetic activity

Energy balance is regulated by neural circuits that integrate peripheral and central stimuli, which, in turn, regulate energy intake and expenditure. Energy expenditure can be divided into resting metabolic rate (60% to 75%), activity-associated thermogenesis (~20%), and diet-induced thermogenesis (10% to 15%).[50] Diet-induced thermogenesis comprises energy expenditure by digestion, absorption, and storage of food and can be affected by the type of food ingested. For example, meals with high protein or carbohydrate content increase diet-induced thermogenesis more than do meals high in fat.[51] The sympathetic nervous system contributes to all three aspects of energy expenditure and is influenced by the hypothalamus.[52]

When melanocortin receptors in the VMH are stimulated, an increase in energy expenditure and physical activity occurs.[53] Activation of these receptors also increases the sympathetic nervous system outflow to skeletal muscles. Moreover, lesions in the VMH or dorsomedial hypothalamus can decrease core body temperature.[54] These effects may be partially mediated by leptin. The hypothalamus (*i.e.*, the dorsomedial hypothalamus, VMH, and arcuate nucleus) expresses high levels of leptin receptors that, when stimulated, increase blood pressure, heart rate, and body temperature.[55,56] Considerably higher leptin levels occur in patients with CP than in the control population.[57] This may be explained by disturbed feedback between the hypothalamus and adipose tissue and suggests that a damaged hypothalamus may be relatively insensitive to leptin.[58] This relative leptin resistance in obesity may contribute to reduced sympathetic nervous system tone.[59]

Thyroid metabolism is another important factor that influences both resting metabolic rate and thermogenesis.[60] Neurons expressing TSH-releasing hormone (TRH) found in the PVN directly regulate thyroid-stimulating hormone secretion in the pituitary gland and thereby thyroid metabolism.T3 and thyroxine T4 directly affect thermogenesis via thyroid hormone receptor-α and lipid metabolism via thyroid hormone receptor-β.[61] In addition to these peripherally mediated actions, hypothalamic nuclei sensitive to thyroid hormones can directly influence energy metabolism. Thyroid hormones within the hypothalamus can stimulate T3-sensitive neurons in the PVN, thereby influencing the sympathetic outflow to the liver and, in turn, modulating endogenous glucose production and hepatic insulin sensitivity.[62] Finally, thyroid

hormones can stimulate energy expenditure in brown adipose tissue (BAT) via the VMH.[63] BAT is a specific tissue for nonshivering thermogenesis that produces heat through uncoupling protein 1 in mitochondria.[64] In addition to cold-induced thermogenesis, thyroid hormones and other signals, such as GLP-1 and leptin, act on BAT through the same pathway.[65,66] The activation of BAT is an interesting target for weight loss because glucose (stored as glycogen) and fatty acids (stored as triglycerides) are used as energy for thermogenesis via uncoupling protein 1. Therefore, the hypothalamus is a key regulator of energy expenditure by influencing many different pathways, including sympathetic nervous system tone, body temperature, thyroid metabolism, and BAT activity.

Role of the hypothalamus in parasympathetic activity

The hypothalamus contributes to parasympathetic activity, including glucose metabolism. Hypothalamic damage may result in disinhibition of parasympathetic signaling, resulting in hyperinsulinemia. This is supported by the finding that supradiaphragmatic vagotomy blunts acute hyperinsulinemia in rats with lesions in the VMH.[67] Increased insulin secretion, in turn, increases calorie storage within adipocytes, thereby leading to body fat accumulation. Several pathophysiologic mechanisms that contribute to hyperinsulinemia have been proposed.[68] Parasympathetic signals from the LHA promote depolarization of pancreatic β-cells by vagus nerve–mediated acetylcholine that acts through M3 muscarinic receptors.[69] β-cell depolarization augments calcium influx and results in insulin hypersecretion. Furthermore, vagus nerve–mediated acetylcholine increases phospholipases within β cells, which may eventually increase intracellular calcium and promote insulin secretion. Increased parasympathetic nervous system tone to the pancreas is associated with increased β-cell proliferation and mass, indicating that both secretion and total β-cell number are regulated by vagal control.[70]

The arcuate nucleus is sensitive to insulin, leptin, and glucose and sends signals to the PVN that subsequently integrate and forward signals to other hypothalamic nuclei or peripheral organs. Activation of insulin receptors in the hypothalamus, specifically the arcuate nucleus, also leads to ATP-sensitive K^+ channel activation, which downregulates gluconeogenesis in the liver via the vagal pathway.[71] A subpopulation of VMH neurons expresses insulin receptors, resulting in feelings of satiety when circulating insulin levels are high.[72] Glucose-sensing neurons are located in the VMH and arcuate nucleus. As brain glucose levels increase, glucose-excited neurons increase their firing rate, whereas glucose-inhibited neurons decrease their action potential frequency.[73] Although these neurons may protect the brain from hypoglycemia, hypothalamic damage may impair their function, leading to inadequate sensing of intracerebral glucose concentrations. In summary, increased parasympathetic nervous system tone, resulting in vagus nerve–mediated hyperinsulinemia and fat accumulation, occurs when the hypothalamus

is damaged. Furthermore, disruption in glucose, insulin, and leptin sensing due to damaged hypothalamic nuclei may result in inappropriate sensing of energy deficits.

Clinical consequences of hypothalamic damage

Destruction of hypothalamic nuclei may cause specific clinical symptoms that contribute to the development of HO in individual patients with CP and other suprasellar tumors.[74] Recognition of these symptoms may lead to identification of the pathophysiologic pathways that are disrupted and can be used as a starting point for an individualized targeted intervention. The specific clinical symptoms that may contribute to HO can be subdivided into six distinct domains: (1) psychosocial disorders, (2) hyperphagia, (3) sleep disturbances, (4) decreased energy expenditure, (5) hyperinsulinemia, and (6) hypopituitarism. In many patients with CP or in survivors with other suprasellar tumors, symptoms across different clinical domains are present simultaneously. In this case, interventions targeting each domain may be combined. By exploring the symptoms reported by patients, the different domains affected by the sellar or suprasellar tumors can be recognized.

Domain 1: Psychosocial disorders

The psychosocial domain comprises psychologic and psychiatric disorders. In patients with CP, behavioral disturbances, impaired social, emotional, and neurocognitive functioning, and overall reduced QoL are often observed, with an overall prevalence of neurobehavioral dysfunction in 57% of patients.[75]

Specific behavioral disorders with disrupted impulse control, aggressiveness, and episodic rage can occur following hypothalamic lesions in both mice and humans.[76-78] Male rats with lesions in the medial hypothalamus aggressively defend their food from other rats.[79] In humans, aggressive behavior caused by hypothalamic damage is reported when access to food becomes restricted.[80] Social abilities, as well as emotional and social adaptation, develop from early childhood to adulthood and are attributed to prefrontal structure. In patients with CP, damage to the prefrontal cortex or projections between the hypothalamus and the prefrontal cortex may occur from tumor or surgical damage, especially when a subfrontal approach is used.[81] Damage to this area may therefore result in disturbances of social abilities or emotions, such as bursts of unpredictable anger.[82] Oxytocin plays an important role in social behavior and learning. Patients with Prader-Willi syndrome and HO and impulsive eating disorders exhibit markedly reduced oxytocin-containing neurons in the PVN, potentially leading to aberrant social behavior (*i.e.* temper outbursts and stubbornness) and hyperphagia.[30] Patients with CP who are obese may also experience decreased oxytocin levels.[83,84]

Damage to adjacent midline structures, such as other limbic structures or the third ventricle, by the tumor, increased intracranial pressure, or cranial radiotherapy may also be partly responsible

for the behavioral and cognitive changes observed in patients with CP or in survivors of other suprasellar tumors.[85] Patients with CP are more likely to demonstrate changes in attention than are other patients with brain tumors.[86] Additionally, IQ scores are related to the volume of the irradiated brain and surgical factors (*i.e.*, extent, number, and postoperative diabetes insipidus).[87] Patients with CP also generally report reduced health-related QoL and impaired psychosocial health.[86,88,89] Patient QoL is associated with tumor biology (*e.g.*, relapse and hypothalamic involvement), tumor treatment (*e.g.*, repeated surgeries and radiotherapy), and the consequences of the tumor or treatment (*e.g.*, vision loss, obesity, hypopituitarism, epilepsy, and pain).[5,90] Abnormalities in mood, such as depression and anxiety, have been reported, although these findings were not specific for CP, as impaired outcomes were also observed in patients with nonfunctioning pituitary adenomas.[91]

Domain 2: Hyperphagia

Lesions of the hypothalamus may lead to inappropriate feelings of hunger, which, in combination with impulse disorders, can result in food cravings and overeating. Although distinct hypothalamic nuclei integrate satiety signals from peripheral and central origins, the VMH and arcuate nucleus are thought to play the most important roles. Rats with VMH lesions are hyperphagic and overweight and develop obesity when food is not restricted.[92]

Additionally, damage of the hypothalamus results in imbalances of appetite-regulating hormones. A reduced sympathetic tone in patients with CP may increase hyperleptinemia, as noradrenaline typically inhibits the release of leptin.[93,94] Moreover, flattened postmeal responses for PYY and ghrelin occur in patients with CP, compared with obese controls, which is most likely caused by dysregulation of the autonomic nervous system.[95] However, baseline ghrelin levels do not appear to differ between patients with CP and obese controls, indicating that hyperghrelinemia, as seen in patients with Prader-Willi syndrome, is not a major contributor to CP-mediated HO.[96] Moreover, CCK levels are not altered in patients with CP or nonfunctioning pituitary adenomas.[97] However, note that these findings are partially contradictory among different studies, which may reflect the heterogeneity of the study populations. Because not all patients with CP develop hyperphagia, this clinical heterogeneity may also reflect specific hypothalamic nuclei that are still intact in some patients.

Several studies have demonstrated equal or less energy intake in both pediatric and adult patients with CP than in the general population.[98-100] However, one study demonstrated pathologic eating behavior in patients with CP who are severely obese, as compared with obese or healthy-weight patients.[101] Although hyperphagia is not a general finding among studies, assessments of food intake are generally challenging, as the reliability and compliance to complete food diaries by patients with CP may not be high (see assessment of hyperphagia below). Additionally, some

patients with CP may have already reached the plateau phase of their weight gain, in which energy intake and expenditure are balanced.

Domain 3: Sleep disturbances

The suprachiasmatic nuclei are key regulators of the circadian rhythm, affecting sleep and wakefulness. The circadian rhythm is mainly influenced by melatonin excretion of the pineal gland during darkness.[102] Alteration in melatonin secretion occurs in patients with CP. Decreased nighttime melatonin and increased cortisol concentrations are associated with decreased total sleep time, time of sleep, sleep efficiency, daytime physical activity, and increased frequency of awakening in patients with CP.[103] A study demonstrated that morning and nighttime melatonin levels are negatively correlated with body mass index (BMI) and daytime somnolence.[104] No differences were observed in midday or evening melatonin concentrations between healthy-weight patients with CP and healthy controls.

In addition to the suprachiasmatic nuclei, the ventrolateral preoptic area and median preoptic nuclei are other important regions for sleep regulation.[105] These nuclei contain sleep-active neurons, such as γ-aminobutyric acid–ergic neurons. Activation of these neurons promotes sleep via descending projections on the LHA, posterior hypothalamus, and brainstem.[106] Arousal pathways are located in the orexin-expressing neurons of the LHA and directly excite the cerebral cortex.[107] The sleep-promoting pathways and arousal pathways can mutually influence each other by a mechanism termed the "flip-flop" switch.[108] This interaction rapidly promotes the transition between waking and sleeping. Lesions of the preoptic area produce insomnia, and lesions of the LHA result in hyposomnia.[109,110] Narcolepsy is a condition characterized by excessive daytime sleepiness, sometimes with concomitant sleep paralysis, hallucinations, and episodes of cataplexy. Interestingly, low orexin levels are present in a subset of patients with narcolepsy, resulting in a destabilized flip-flop switch.[111] Although orexin-producing neurons are located in the hypothalamus, just a few studies, consisting primarily of case reports, have reported the presence of secondary narcolepsy following brain tumors.[112] A recent large study reported a prevalence rate of 1670 per 100,000 for hypersomnia/narcolepsy in childhood brain tumor survivors.[113] This prevalence was most likely underestimated because not all survivors in the study received a systematic sleep assessment. In this study, the risk of hypersomnia and narcolepsy was associated with midline tumors, radiation doses > 30 Gy, and anti-epilepsy drug use. The high prevalence of daytime sleepiness in up to one-third of patients with CP may contribute to HO by reducing daily activity, and this effect may be exacerbated because sleep deprivation stimulates appetite.[104,114] Additional factors may influence poor quality of sleep and daytime somnolence, such as suboptimal timing or substitution of pituitary deficiencies, fatigue due to the previous tumor (treatment), and psychosocial disorders.

Domain 4: Decreased energy expenditure

Hypothalamic lesions may cause decreased sympathetic activity, resulting in overall reduced metabolic activity. Heart rate, blood pressure, and body temperature are all influenced by the hypothalamus. Simultaneous reductions in resting metabolic rate and decreased physical activity may contribute to HO. Indeed, patients with CP exhibit markedly lower physical activity levels than do obese (matched) controls from the general population.[98-100] Pediatric patients with CP exhibit decreased resting energy expenditures than do children with multifactorial obesity, which does not result from differences in body composition.[115] This is supported by a study that noted lower basal metabolic rates, even after adjusting for lean mass, in patients with CP.[100] Moreover, patients with CP have decreased catecholamine levels, indicative of decreased sympathetic tone.[116] In general, reduced sympathetic tone may contribute to reduced resting metabolic rates.

Stimulation of the VMH in rats increases metabolism, and a damaged VMH will ostensibly lead to a decreased metabolic rate.[117] Thyroid hormones also influence basal metabolic rate and energy expenditure. Attenuated thyroid hormone levels decrease total body energy expenditures. During fasting or caloric restriction, reduced circulating thyroid hormone levels generate an adaptive decrease in energy expenditure. This may be caused centrally by decreased leptin concentrations that, in turn, suppress expression of TRH-expressing neurons in the PVN, partially via NPY-expressing neurons. Additionally, neurons expressing the MC4R and NPY are required to activate the hepatic circuit to metabolize thyroid hormones.[118] Other factors may contribute to decreased energy expenditures in patients with CP and other suprasellar tumors, such as daytime somnolence, vision loss, neurologic deficits, and obesity itself. Additionally, oversubstitution or undersubstitution of hormone replacement therapy can cause symptoms of fatigue and decreases in activity levels.

Domain 5: Hyperinsulinemia

Upregulation of parasympathetic activity in patients with CP may lead to vagus nerve stimulation of the pancreas, resulting in hyperinsulinemia. This occurs primarily in response to glucose, especially in patients with CP-induced HO, resulting in very efficient, although undesirable, storage of fat from ingested foods.[119] Fasting insulin concentrations may be similar in patients with CP as in obese children from the general population.[57,120] A positive correlation was observed between preoperative plasma fasting insulin concentrations and weight change during the first year after surgery in patients with CP.[121] Therefore, in patients with CP who are obese, hyperinsulinemia may be primarily caused by disturbed autonomic regulation of vagal tone, but it may also be the consequence of insulin resistance levels comparable to those of obese persons in the general population. Insulin resistance, often defined by homeostasis model assessment of insulin resistance (HOMA-IR), is not as high in patients with CP as it is in the general obese

population.[119] Additionally, the degree of hypothalamic involvement apparently influences insulin resistance, as HOMA-IR is higher in patients with marked tumor involvement, regardless of BMI.[122]

Domain 6: Hypopituitarism

The PVN is the key regulator of the pituitary gland. The pituitary gland, in turn, secretes distinct hormones that exert direct metabolic effects or stimulate peripheral endocrine organs to produce other hormones. GH, thyroid hormones, and testosterone are notable stimulants of the metabolic system. Neurons of the PVN project to the median eminence, where nerve terminals release the pituitary-stimulating hormones TRH and corticotropin-releasing hormone at the capillary plexus of the hypophyseal portal system. Thyroid hormones directly affect thermogenesis and metabolic rate. Neurons expressing GH–releasing hormone are primarily located in the arcuate nucleus and stimulate the pituitary gland to secrete GH. GH exerts many direct metabolic effects, such as increasing protein synthesis, increasing the rate of lipolysis, decreasing glucose uptake into cells (glucose-sparing effect), increasing transport of amino acids into cells, and increasing transcription and translation by cells.[123] All of these effects result in growth of cells and improvement of body composition.

Neurons expressing GnRH may be localized to different hypothalamic regions, as they arise from multiple embryonic origins and migrate primarily to anterior regions of the hypothalamus (*e.g.*, the preoptic area).[124] Testosterone influences resting energy expenditure by increasing muscle mass. In addition to affecting body composition, pituitary hormones may affect bone mineral density (BMD). In general, obesity and female sex are protective against low BMD. However, female patients with CP have considerably lower BMD than do matched population controls, whereas male patients do not, despite similarities in pituitary deficiencies and substitution therapy.[125] This suggests that female patients would benefit from timely induction of puberty by estrogen replacement therapy to reach peak bone mass.

Depletion of GH, thyroid hormones, and testosterone may increase body weight, alter body composition, and negatively affect bone health. In contrast, high cortisol concentrations (endogenous or exogenous supplementation) can promote weight gain. In a study by Müller *et al.*, the dose and duration of perioperative dexamethasone influenced weight gain postoperatively, although long-term effects on weight gain were not observed.[126] It is suggested that patients with CP may require smaller doses of glucocorticoid replacement because of upregulated 11β-hydroxysteroid dehydrogenase activity that increases conversion of cortisone to cortisol.[127] To optimize bone health, quality of sleep, and the metabolic state, appropriate management of hydrocortisone substitution therapy is necessary.

Systematic review for hypothalamic obesity interventions in patients with craniopharyngioma and other suprasellar tumors

Methods

We performed a systematic review of HO interventions for patients with CP and other suprasellar tumors, according to the published guidelines for the conduct of systematic reviews of interventions and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[128]

Study inclusion criteria

Studies containing humans of any age with a history of CP or other suprasellar tumors, who received a potential weight-reducing intervention, were included. The study population included at least 50% patients with CP or suprasellar tumors. Thus, the etiology for HO (*i.e.*, acquired damage to the hypothalamus in patients with suprasellar tumors) was captured. Studies in which >50% of patients had HO due to other pathophysiologic mechanisms, such as head trauma, single genetic mutations, genetic syndromes, inflammation, or cerebral aneurysm, were excluded. We placed no restrictions on the minimum number of patients included in the intervention studies. However, because a large number of studies reviewed the use of GH for metabolic outcomes, we excluded GH intervention studies conducted with <100 patients.

Interventions aiming for weight reduction, weight stabilization, or weight gain stabilization were included. Primary outcome or secondary outcomes reported descriptive characteristics or quantitative measurements on weight, such as BMI, BMI z score/SD score (SDS), absolute weight (kg), and/or changes in weight (%, Δ, SDS, or kg). We considered all types of weight management interventions, including psychologic and dietary interventions, pharmacotherapeutic agents, and surgical procedures.

Report characteristics

Randomized controlled trials (RCTs), observational studies, cohort studies, case-control studies, and case series or reports published in English, German, or Dutch were included. For duplicates of the same study cohorts, in which the same intervention was applied, we included the most recent publication. Conference abstracts and reviews were excluded.

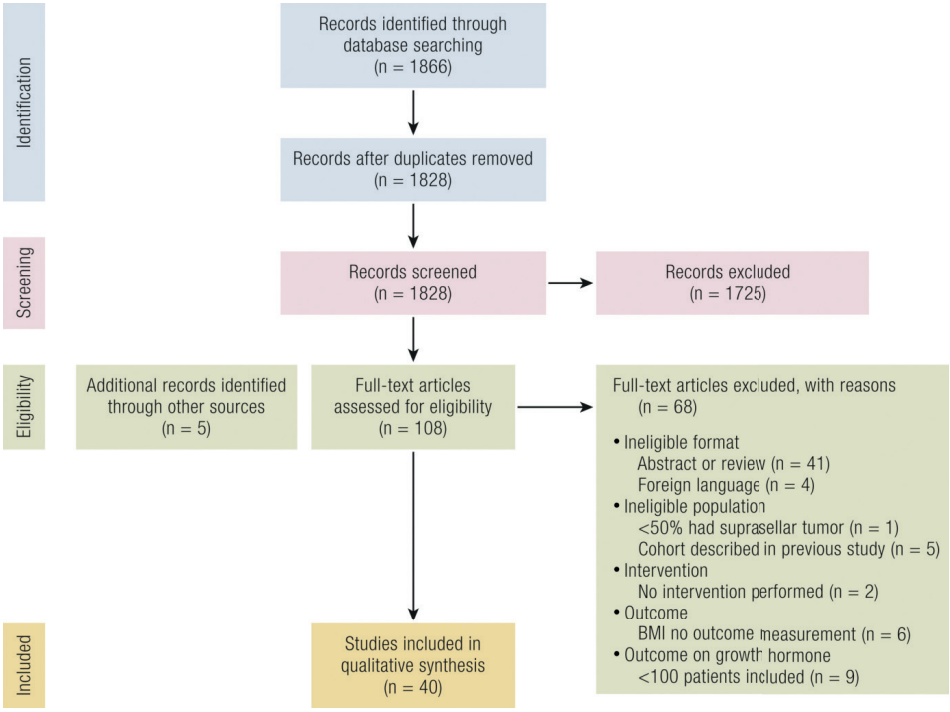
Search strategy

Two librarians designed the literature search with input from the authors. The systematic literature searches were completed on 12 September 2017, by using two electronic databases (MEDLINE and Embase). The database searches spanned studies without restrictions on language, study design, or date of publication. The following search terms were used, with adaptation for each database: craniopharyngioma; hypothalamic tumor; body weight; body mass index; weight gain; weight reduction. Our detailed search strategy is described in Supplemental Table 1.

Study selection

All titles or abstracts were reviewed independently by two reviewers. Any discrepancies in the inclusion or exclusion of studies were discussed until a consensus was achieved. If disagreement persisted, a third reviewer was consulted. Full-text studies were obtained from those references with titles or abstracts that potentially matched the inclusion criteria. Additional studies were identified by a manual backward tracking search of the reference list of included studies and a forward citation search via Web of Science. The selection process is outlined in Figure 2.

Figure 2. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flowchart of study selection



Data extraction

Data from each included study were extracted in duplicate by two independent investigators by using a piloted data extraction form based on the Cochrane Consumers and Communication Review Group data extraction template for included Studies.[129] This data extraction form was tested on five randomly selected included studies and, after minor adjustments, was used to extract data from all included studies. Extracted data were cross-checked by a second reviewer. The extracted data included the following details: (1) patient demographics (*e.g.*, age, sex, total number of patients with CP or other suprasellar tumors, and total number of control patients),

(2) study design, (3) type and duration of intervention, (4) follow-up duration, (5) effect of the intervention on outcome measures, (6) adverse effects, (7) participant withdrawal, and (8) responders (*i.e.*, beneficial effect of intervention on weight) and nonresponders (*i.e.*, no beneficial effect of intervention on weight). We proposed to combine the results of these studies in a meta-analysis if three or more studies with comparable study designs within the same clinical domain were included.

Assessment of study quality

Two reviewers independently assessed the risk of study bias by using the Cochrane risk of bias assessment tool for RCTs.[130] For nonrandomized studies of interventions, the Risk of Bias in Nonrandomized Studies of Interventions tool was used.[131] Uncontrolled observational studies and case reports/series were *a priori* considered to be at very serious risk of bias and were therefore not assessed with a specific tool.

Overall quality of evidence

The overall quality of evidence was assessed per outcome by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool.[132] The GradePRO Web application was used to create an evidence table, including certainty assessment and summary of findings.[133] Subsequently, the available evidence was combined and translated into recommendations. The development of a recommendation was considered when two or more studies with comparable study designs within the same clinical domain were included. The GRADE tool was also used to assess the strength of recommendations (*i.e.*, strong or weak) by combining information on the quality of the evidence, the balance between desirable and undesirable outcomes, patient values and preferences, and resources (*i.e.*, costs vs benefits).[134]

Results

Study selection

The systematic search yielded 1866 publications from the two databases. Thirty-eight duplicated reports were excluded, resulting in 1828 records. On the basis of the titles and abstracts, 1725 publications were excluded. Of the 103 remaining publications, full-text articles were obtained. Five additional articles were identified through backward and forward reference screening. Of the total 108 full-text articles, 40 were included in the final analysis, according to the previously established inclusion criteria. A flowchart of the systematic literature search is shown in Figure 2.

Description of included studies

The systematic review identified three double-blind, placebo-controlled trials[135-137], five prospective open-label studies[138-142], one prospective cohort study[143], eight retrospective cohort studies with five or more patients[144-151], and 23 case series reporting one to four cases[80,152-173]. Study characteristics are summarized in Tables 1–4.

Table 1. Descriptive characteristics of studies with lifestyle interventions

First Author, Year of Publication	Population (Sex)	Age at CP Diagnosis (y)	Age of Cohort at Intervention	Comparison Population	Description of Intervention	Preintervention Weight (Intervention Group)
Meijneke *et al.*, 2015 (152)	One patient with CP (F)	5.5	Child	—	Pediatric hospital	BMI, 51.8 kg/m^2
Skorzewska *et al.*, 1989 (80)	Two patients with CP (50.0% M)	Range, 2–12	Child	—	Psychiatric hospital	Weight, 64 kg, 59 kg
Sterkenburg *et al.*, 2014 (145)	31 patients with CP (38.7% M)	Median, 9.19 (range, 1.93–17.42)	Child	77 patients with CP; child; (49.4% M)	Rehabilitation program	Median BMI SDS, 1.32 (range, −1.08 to 7.00)
Rakhshani *et al.*, 2010 (143)	39 patients (40% M), 84.6% CP	Median, 7.6 (range, 2.2–15.9)	Child	—	Specialized outpatient clinic	Median BMI, 28.6 kg/m^2 (range, 16–45.6)
						Median BMI SDS, 1.93 (range, 0–3.2)
						Median weight gain/y, 21.4% (range, 15.8–32.0)
Steele *et al.*, 2013 (144)	77 patients (55.8% M), % CP unknown	Mean, 44 (SD, 16.5)	Adult	—	Specialized outpatient clinic	Median BMI, 28.1 kg/m^2; IQR, 24.3–32.4 kg/m^2

Table 1. Continued

Preintervention Weight (Comparison Group)	Follow-Up Time (Range)	Weight at Follow-Up (Intervention Group)	Weight at Follow-Up (Comparison Group)	Adverse Events or Withdrawal	Intervention Response	Risk of Bias
—	8 wk	Weight loss, 10 kg	—	None reported	Weight reduction (responder), then gain after hospital discharge	Very serious
—	2-y hospitalization/8-y follow-up after surgery; 7-y hospitalization	Weight, 97 kg, 97.7 kg	—	None reported	Weight gain (nonresponders), especially during weekends in home environment	Very serious
Median BMI SDS, 0.23 (range, −2.67 to 6.98)	Intervention group: 39 d (range, 20–135) rehabilitation; follow-up, 10.78 y (range, 10.52–27.56). Comparison group: follow-up, 16.18 y (range, 9.81–36.35)	Median BMI SDS, 4.92 (range, −0.20 to 13.13)	Median BMI SDS, 2.09 (range, −1.48 to 10.23)	None reported	Weight gain in intervention and comparison groups (responder information unreported)	Serious
—	Mean, 0.97 y (range, 3–41 mo)	Median BMI, 30.8 kg/m^2 (range, 18.1–49.1)	—	None reported	Significantly decreased weight gain/y (responder information unreported)	Very serious
		Median BMI SDS, 2.03 (range, −0.2 to 2.6)				
		Median weight gain/y, 8.5% (range, 3.4–14.0)				
—	Median, 9 y	Median BMI, 32 kg/m^2 (IQR, 27.7–38.38 kg/m^2)	—	None reported	Significant weight gain in total cohort, 54.5% had new or worsened obesity (nonresponders), and 45.5% had no weight gain (responders)	Very serious

Abbreviations; IQR, interquartile range

Table 2. Descriptive characteristics of studies with dietary interventions

First Author, Year of Publication	Population (Sex)	Age at CP Diagnosis (y)	Age of Cohort at Intervention	Comparison Population	Description of Intervention	Preintervention Weight (Intervention Group)	Preintervention Weight (Comparison Group)	Follow-Up Time (Range)	Weight at Follow-Up (Intervention Group)	Weight at Follow-Up (Comparison Group)	Adverse Events or Withdrawal	Intervention Response	Risk of Bias
Lee *et al*, 1992 (153)	One patient with CP (M)	7.9	Child	—	PSMF diet	BMI, 47.0 kg/m^2; weight, 109 kg	—	9 mo	BMI, unknown; weight, 71 kg	—	None reported	Weight reduction (responder), then suspected gain after stopping diet	Very serious

Participants

Twenty-nine studies included patients with childhood or adolescent (up to the age of 21 years) onset of CP or suprasellar tumors[80,135,137-141,143,145-147,149,151-153,156-164,166-169,173]. Four studies included only patients with adult onset of CP or suprasellar tumors[144,154,155,165], and another five studies included patients with either childhood or adult onset of suprasellar tumors or CP[142,148,150,170,171]. In two studies, the onset of CP was not described[136,172]. In total, 14 studies included children (≤18 years of age)[80,135,138-141,143,145,147,152,153,156,157,168], 19 studies included adults (>18 years of age)[136,142,144,148,150,151,154,155,158-165,170,171,173], and seven studies included both children and adults.[137,146,149,166,167,169,172] The included studies recruited 1827 participants (51.0% male) in total, of which 777 received an intervention, and the remaining 1050 participants were included as comparison controls. The sample size of the intervention group ranged from one to 260 patients in each study. In 24 studies, only patients with CP were included, whereas 11 studies included other causes for HO or excessive weight gain. Five case reports/series included only patients with other hypothalamic tumors. [154,158,159,165,167] The other entities deemed causative for HO included in the studies were other tumors (*i.e.*, suprasellar germinoma, lipoma, hamartoma, optic glioma, pituitary adenoma, histiocytosis X, astrocytoma, pineal germ cell tumor, choristoma, epidermoid cyst, or other unspecified hypothalamic tumors), pituitary necrosis, or cranial radiotherapy for acute lymphocytic leukemia. In eight studies, an intervention group was compared with a control population, consisting of patients with suprasellar tumors in six studies[135-137,145,147,151] or with the general population in two studies.[149,150]

Interventions

Within the 40 included studies, four main intervention groups were identified: lifestyle[80,143-145,152], dietary[153], pharmacotherapeutic (n = 22), or surgical (n = 12). The pharmacotherapeutic interventions comprised four categories: (1) stimulants, such as dextroamphetamine[138,146], methylphenidate[156], mazindol[155], caffeine, and ephedrine[166], and supraphysiologic T3 supplementation[157,167]; (2) antidiabetic agents, such as metformin combined with micronized fenofibrate, pioglitazone, or diazoxide[139,140,165], diazoxide monotherapy[137], and GLP-1 agonists[142,148,158-160]; (3) hypothalamic-pituitary substitution therapy[147,151]; and (4) other agents, including octreotide[135,141], fluoxetine, and fenfluramine[154], or methionine aminopeptidase 2 (MetAP2) inhibitors.[136] Surgical interventions included bariatric surgery, such as laparoscopic adjustable gastric banding (LAGB)[169]; sleeve gastrectomy (SG)[173]; gastric bypass surgery[161,162,172]; or a combination of LAGB, SG, gastric bypass surgery, or biliopancreatic derivation gastric surgery.[149,150,168,170,171] Other surgical interventions included truncal vagotomy[163] and implantation of a deep-brain stimulation (DBS) electrode to stimulate the nucleus accumbens bilaterally.[164] Because of high heterogeneity between these studies, we did not perform any meta-analyses.

Outcomes

Various weight change outcomes were used in the included studies: BMI (absolute and z score/SDS), absolute weight (kg), or weight change (kg, kg/m^2, %, or SDS). In one study, the descriptive effects of the weight intervention were reported, but no absolute numbers were provided.[157] In another study, the descriptive outcomes after bariatric surgery were reported, but the absolute numbers defining the outcomes were only visible in the figures.[149] Secondary outcomes of interest that covered one or more of the six clinical domains included changes in neuropsychologic functioning, appetite, or food intake; sleep disturbances (*e.g.*, daytime somnolence); markers of physical activity; energy expenditure; and hyperinsulinemia. We analyzed these data according to the type of intervention (*i.e.*, lifestyle, dietary, pharmacotherapeutic, or surgical interventions) and the clinical domain targeted (*i.e.*, psychosocial disorders, hyperphagia, sleep disturbances, decreased energy expenditure, hyperinsulinemia, or hypopituitarism). For each intervention, the number of responders vs nonresponders was retrieved from the study when this information was available. Responders were defined as patients who experienced weight reduction or weight stabilization after the intervention.

Risk of bias

We assessed the risk of bias for three RCTs with the Cochrane risk of assessment tool (Supplemental Figure 1).[135-137] We found the risk of bias to be low for the RCT reported by Shoemaker *et al.*, unclear for that reported by Lustig *et al.*, and high for that reported by Brauner *et al.* We assessed the risk of bias for five nonrandomized controlled intervention studies with the Risk of Bias in Nonrandomized Studies of Interventions tool (Supplemental Table 2).[145,147,149-151] We found all five of these studies to be at high risk of bias because possible confounding factors were not included in the final analyses. We found the remaining uncontrolled observational studies and case reports/series (n = 32) to be at very high risk of bias. The risk of bias for each individual study is shown in Tables 1–4.

Quality of evidence

All outcomes assessed with the GRADE methodology demonstrated very low quality of evidence (Supplemental Table 3). We assessed the studies across five domains: risk of bias, consistency, directness, precision, and reporting bias. We found most studies to be at high or very high risk of bias (due to insufficient descriptions of randomization methods), to contain inconsistencies (*e.g.*, conflicting results between studies), and to be imprecise (*e.g.*, small studies with descriptive results).

Recommendations

The recommendations we generated in this review are based on either the findings reported in the studies included in our systematic review or on existing guidelines or expert opinion when evidence was considered insufficient. The strengths of each recommendation translated

from the evidence reported in the included studies are summarized in Supplemental Table 4. The strengths of all recommendations were weak, primarily because of a lack of good-quality evidence. We did not assess the strengths of the recommendations based on existing guidelines because these used many different grading systems. However, we referred to the original guidelines to infer their quality.

Weight outcomes according to type of intervention

Lifestyle interventions

In total, five studies included lifestyle interventions[80,143-145,152] (Table 1). After hospitalization, only one of three patients experienced weight loss, although weight gain was observed after all patients returned to their home environment.[80,152] A retrospective study reported that BMIs after a follow-up period >10 years were higher in patients who underwent rehabilitation than in patients without rehabilitation.[145] A prospective cohort study demonstrated significantly less weight gain in patients after visiting a neuroendocrinology clinic that provided personalized lifestyle advice within a multidisciplinary team.[143] A large retrospective study reported increased BMIs in a cohort of patients with CP after attending a neuroendocrinology clinic.[144] However, of all patients, 42 (54.4%) experienced new or worsened obesity (nonresponders), and 35 (45.5%) exhibited no weight gain (responders). Patients with new or worsened obesity were more likely to receive hormone replacement than were patients without weight gain. This association likely reflects a greater degree of hypothalamic damage. In three of the five studies, the specific numbers of responders vs nonresponders could be retrieved. Only one of three (33%) of hospitalized patients (responders) demonstrated weight reduction. No adverse events were reported for all five lifestyle intervention studies.

Dietary intervention

Although many of the included studies reported failure of weight loss after lifestyle interventions, only one study reported the effect of a dietary intervention in sufficient detail (Table 2). In one male patient with CP who exhibited hyperphagia and excessive weight gain (+62 kg in ~4.5 years after initial CP surgery), a protein-sparing modified fast (PSMF) program resulted in weight loss during 9 months of follow-up (responder). However, after discontinuation of PSMF, we suspect weight gain ensued. This was graphically shown, but no long-term (descriptive) follow-up data were reported. No adverse events were reported during use of the PSMF.

Pharmacotherapeutic interventions

In total, 20 intervention studies were identified that reported the effect of pharmacotherapeutic agents on HO (Table 3).

Table 3. Descriptive characteristics of studies with pharmacotherapeutic interventions

First Author, Year of Publication	Population (Sex)	Age at CP Diagnosis (y)	Age of Cohort at Intervention	Comparison Population	Description of Intervention	Preintervention Weight (Intervention Group)	Preintervention Weight (Comparison Group)	Follow-Up Time (Range)	Weight at Follow-Up (Intervention Group)	Weight at Follow-Up (Comparison Group)	Adverse Events or Withdrawal	Intervention Response	Risk of Bias
Mason *et al.*, 2002 (138)	Five patients with CP (60% M)	Unknown (childhood onset)	Child	—	Dextroamphetamine (5 mg, increased 2.5 mg weekly), mean maximum daily dose of 16 ± 2 mg (Three doses per d)	Mean BMI, 32 kg/m^2 (SD, 2.8) Mean weight gain/mo, 2.0 kg (SD, 0.3)	—	24 mo	Mean BMI, 31 kg/m^2 (SD, 3.3) Mean weight gain/mo, 0.4 kg (SD, 0.2)	—	Headaches (n = 1), enlarged cyst (n = 1)	Significantly stabilized weight gain in all patients (responders)	Very serious
Ismail *et al.*, 2006 (146)	12 Patients, 75% CP (41.7% M)	Median, 9.4 (range, 4.4–13.1)	Child, adult	—	Dextroamphetamine (5 mg, twice daily)	Unknown (only individual weights known)	—	Males Median, 13 mo (range, 7–63) Females Median, 15 mo (range, 6–48)	Decreased median weight SDS (−0.7 in males, −0.44 in females)	—	Insomnia (n = 1), tumor recurrence, study withdrawal (n = 1)	Weight loss or stabilized weight gain (10 of 12 patients) (responders)	Very serious
Elfers and Roth, 2011 (156)	One patient with CP (M)	5.9	Child	—	Methylphenidate (20 mg/d, gradual increase to 50 mg/d, and 60 mg/d after 31 wk)	BMI, 45.5 kg/m^2 BMI z score, +2.9 Weight, 154 kg	—	87 wk	BMI, 41.4 kg/m^2 BMI z score, +2.8 Weight, 142 kg	—	None reported	Reduced BMI (responder)	Very serious
Sadatomo *et al.*, 2001 (155)	One patient with CP (M)	5.4	Adult	—	Mazindol (0.5 mg/d)	Weight, 70 kg	—	3-wk intervention; 3-y follow-up	Weight, 60 kg (1.5 mo after mazindol withdrawal)	—	None reported	Weight reduction (responder); stable for 3 y without further mazindol administration	Very serious
Greenway and Bray, 2008 (166)	Three patients, 66.7% CP (0% M)	Range, 4–8	Child, adult	—	Caffeine (200 mg) and ephedrine hydrochloride (25 mg) (during 2 wk, increased to 3 times/d)	BMI, 41.4 kg/m^2, 27.7 kg/m^2, 34.7 kg/m^2 Weight, 116 kg, 77.8 kg, 97.8 kg	—	2-, 6-, and ~5.5-y intervention Outcomes reported after 6 m (range, 3–6)	Weight loss, −8% to −9%, −18.8%, −14% Mean weight loss, 13.9% of body weight	—	Shakiness (n = 1)	Weight reduction in all patients (responders); maintained weight loss (two of three patients)	Very serious
Fernandes *et al.*, 2002 (167)	Three patients, 0% CP (33.3% M)	Range, 3–7	Child, Adult	—	Supraphysiologic T3 (10 μg, 2–3 times/d), increased to 20 μg and 25 μg for two patients	BMI, 28.2 kg/m^2, 25.7 kg/m^2, 25.2 kg/m^2 Weight, 60.8 kg, 48.6 kg, 48.3 kg	—	11- to 27-mo intervention	Weight loss, 14.0 kg, 4.3 kg, 8.1 kg	—	None reported	Weight reduction in all patients (responders)	Very serious
van Santen *et al.*, 2015 (157)	One patient with CP (F)	5.5	Child	—	Supraphysiologic T3 (125 μg, 3 times/d)	Unknown	—	2 mo	Unknown	—	None reported	No BMI change (nonresponder)	Very serious

Table 3. Continued

First Author, Year of Publication	Population (Sex)	Age at CP Diagnosis (y)	Age of Cohort at Intervention	Comparison Population	Description of Intervention	Preintervention Weight (Intervention Group)	Preintervention Weight (Comparison Group)	Follow-Up Time (Range)	Weight at Follow-Up (Intervention Group)	Weight at Follow-Up (Comparison Group)	Adverse Events or Withdrawal	Intervention Response	Risk of Bias
Kalina *et al*, 2015 (140)	22 Patients with CP (45.5% M)	Median, 10.5 (range, 0.17–16.75)	Child	—	Lifestyle intervention in all patients; metformin (500–1500 mg daily) and micronized fenofibrate (160 mg daily) in patients with signs of metabolic syndrome (n = 10)	Median BMI SDS, 1.91 (range, 1.2–2.7)	—	6-mo pharmacotherapeutic intervention	Median BMI SDS, 1.87 (range, 1.3–2.6)	—	None reported	No significant BMI change in total cohort (responder information unreported)	Very serious
Igaki *et al*, 2005 (165)	One patient (F), 0% CP	52	Adult	—	Pioglitazone (15 mg daily) and metformin (500 mg daily increased to 750 mg/d)	BMI, 25 kg/m^2 Weight, 54 kg	—	30-mo intervention	BMI, 25 kg/m^2 Weight, 55 kg	—	None reported	No BMI change (nonresponder)	Very serious
Hamilton *et al*, 2011 (139)	Nine patients with CP (55% M)	Unknown (childhood onset)	Child	—	6-mo prestudy lifestyle intervention; diazoxide (2 mg/kg twice daily, maximum 200 mg/d) and metformin (500 mg twice daily, increased to 1000 mg)	Prestudy: Mean BMI, +2.2 kg/m^2 (SD, 1.5) Mean BMI SDS, +0.11 (SD, 0.08) Mean weight gain, +9.5 kg (SD, 2.7)	—	6-mo intervention	Intervention: Mean BMI, −0.3 kg/m^2 (SD, 2.3) Mean BMI SDS, −0.04 (SD, 0.15) Mean weight gain, +1.2 kg (SD, 5.9)	—	Pedal edema (n = 1), mildly elevated hepatic enzyme levels and vomiting (n = 1); study withdrawal (n = 2)	Weight reduction in three of nine patients (responders)	Very serious
Brauner *et al*, 2016 (137)	18 Patients, % CP unknown (% male unknown)	Unknown (childhood onset)	Child, adult	17 Patients, % CP unknown; child, adult	Diazoxide or placebo (4 mg/kg/d in two doses, adjusted between 3.2 to 4.2 mg/kg/d during trial)	Median BMI z score, 4.1 (IQR, 3–4.7) Median weight, 81 kg (IQR, 71–84)	Median BMI z score, 4.2 (IQR, 3.7–5.2) Median weight, 81 kg (IQR, 57–109)	24-wk intervention	Median BMI z score, 3.8 (IQR, 2.9–4.4) Median weight, 80 kg (IQR, 70–84)	Median BMI z score, 4 (IQR, 3.5–4.7) Median weight, 74.5 kg (IQR, 57.1–109.2)	Diabetes mellitus (n = 3, treatment group, excluded for analysis); hirsutism (n = 9, treatment group; n = 1, placebo group); edema (n = 13, treatment group)	No BMI change (responder information unreported)	Serious
Simmons *et al*, 2012 (158)	One patient (M), 0% CP	17	Adult	—	Exenatide (5 μg twice daily)	BMI, 39.3 kg/m^2 Weight, 111 kg	—	32-mo intervention	BMI, 29.1 kg/m^2 Weight, 81.7 kg	—	None reported	Weight reduction during intervention (responder); weight gain after stopping intervention	Very serious

Table 3. Continued

First Author, Year of Publication	Population (Sex)	Age at CP Diagnosis (y)	Age of Cohort at Intervention	Comparison Population	Description of Intervention	Preintervention Weight (Intervention Group)	Preintervention Weight (Comparison Group)	Follow-Up Time (Range)	Weight at Follow-Up (Intervention Group)	Weight at Follow-Up (Comparison Group)	Adverse Events or Withdrawal	Intervention Response	Risk of Bias
Thondam *et al*, 2012 (159)	One patient (F), 0% CP	9	Adult	—	Exenatide with switch to liraglutide (dosages unknown)	Weight, 148 kg	—	4-y intervention	Weight, 140 kg	—	Occasional nausea	Weight reduction (responder)	Very serious
Castro-Dufourny *et al*, 2017 (160)	One patient with CP (F)	11	Adult	—	Dulaglutide (1.5 mg/wk)	BMI, 34 kg/m^2 Weight, 88 kg	—	2-mo intervention	BMI, 29.97 kg/m^2 Weight, 77.7 kg	—	None reported	Weight reduction (responder)	Very serious
Zoicas *et al*, 2013 (148)	Nine patients (M), 66.6% CP	Range, 19–49	Adult	—	Exenatide (n = 8), 11.4 μg/d (SD, 3.8) or liraglutide (n = 1), 0.6 mg/d	Mean BMI, 37.6 kg/m^2 (SD, 7.2) Mean weight, 120.6 kg (SD, 21.7)	—	Mean 24.3-mo intervention (range, 6–51)	Mean BMI, 33.4 kg/m^2 (SD, 6.3) Mean weight, 107.5 kg (SD, 18.4)	—	Nausea and vomiting (n = 3), study withdrawal (n = 2)	Significantly reduced BMI in total cohort; weight reduction in all patients with > 6 mo of therapy (n = 8) (responders)	Very serious
Lomenick *et al*, 2016 (142)	10 Patients, 60% CP (30% M)	Unknown (60% childhood onset, 40% adult onset)	Adult	—	Exenatide (5 μg, twice daily and increased to 10 μg after 8 wk)	Mean BMI, 47.5 kg/m^2 (SD, 10.8) Mean weight, 138.3 kg (SD, 41.5)	—	50-wk intervention	Mean weight loss, −1.4 kg (SD, −4.3)	—	Nausea/vomiting (n = 7), joint pain (n = 3), and injection site reactions (n = 3); study withdrawal (n = 3) due to increased irritability and mood swings (n = 1), kidney stones (n = 1), or no increase in exentatide dose (n=1)	No significant weight loss in total cohort; stable or decreased weight (n = 6) (responders)	Very serious
Geffner *et al*, 2004 (147)	199 Patients with CP (62.3% M)	Unknown (childhood onset)	Child	92 patients with postsurgical and/or postirradiated GHD (+S/I); child (64.1% M); 85 patients with organic GHD without surgery or radiotherapy (−S/I); child (71.8% M)	GH supplementation, initially 0.17 mg/kg/wk (SD, 0.06), 0.16 mg/kg/wk (SD, 0.07) after 3 y	Mean BMI SDS, 1.26 (SD, 1.51) Mean weight, −0.32 SDS (SD, 1.75)	Comparison (+S/I): Mean BMI SDS, 0.61 (SD, 1.46) Mean weight, −0.98 SDS (SD, 1.77) Comparison (−S/I): Mean BMI SDS, −0.12 (SD, 1.84) Mean weight, −2.33 SDS (SD, 1.98)	3-y intervention	Mean BMI SDS, 1.01 (SD, 1.55) Mean weight, 0.34 SDS (SD, 1.74)	Comparison (+S/I): Mean BMI SDS, 0.35 (SD, 1.71); Mean weight, −0.42 SDS (SD, 2.00) Comparison (−S/I): Mean BMI SDS, 0.29 (SD, 1.69) Mean weight, −0.60 SDS (SD, 1.97)	None reported	Significant weight increase in total cohort, but not in BMI (responder information unreported)	Serious

Table 3. Continued

First Author, Year of Publication	Population (Sex)	Age at CP Diagnosis (y)	Age of Cohort at Intervention	Comparison Population	Description of Intervention	Preintervention Weight (Intervention Group)	Preintervention Weight (Comparison Group)	Follow-Up Time (Range)	Weight at Follow-Up (Intervention Group)	Weight at Follow-Up (Comparison Group)	Adverse Events or Withdrawal	Intervention Response	Risk of Bias
Yuen et al, 2013 (151)	260 Patients with CP (58.5% M)	Unknown (childhood onset)	Adult	433 patients with idiopathic/ congenital hypopituitarism; adult (60.5% M); 112 patients with extrasellar tumors, adult (57.1% M)	GH supplementation, initially 0.3 mg/ d (SD, 0.3)	Males: Mean BMI, 29.5 (SD, 7.2)	Idiopathic/ congenital GHD:	5-year intervention	Males: ΔBMI, 1.4 kg/m^2 (SD, 3.8)	Idiopathic/ congenital GHD:	None reported	Significantly increased BMI (responder information unreported)	Serious
						Mean weight, 90.9 kg (SD, 25.9)	Males		ΔWeight, 6.0 kg (SD, 13.9)	Males			
						Females: Mean BMI, 30.4 (SD, 8.9)	Mean BMI, 24.6 (SD, 4.7)		Females: ΔBMI, 2.3 kg/m^2 (SD, 3.1)	ΔBMI, 1.7 (SD, 2.7)			
						Mean weight, 79.0 (SD, 23.4)	Mean weight, 69.1 kg (SD, 15.0)		ΔWeight, 7.7 kg (SD, 9.2)	ΔWeight, 5.4 (SD, 7.7)			
							Females			Females			
							Mean BMI, 24.9 (SD, 6.6)			ΔBMI, 1.1 (SD, 3.7)			
							Mean weight, 60.0 (SD, 15.4)			ΔWeight, 3.3 kg (SD, 8.8)			
							Extrasellar tumors:			Extrasellar tumors			
							Males			Males			
							Mean BMI, 25.2 (SD, 5.5)			ΔBMI, 1.2 (SD, 1.5)			
							Mean weight, 71.6 kg (SD, 21.6)			ΔWeight, 3.9 (SD, 5.0)			
							Females			Females			
							Mean BMI, 26.7 (SD, 6.7)			ΔBMI, 0.8 (SD, 5.1)			
							Mean weight, 64.1 (SD, 15.8)			ΔWeight, 3.2 kg (SD, 10.2)			

Table 3. Continued

First Author, Year of Publication	Population (Sex)	Age at CP Diagnosis (y)	Age of Cohort at Intervention	Comparison Population	Description of Intervention	Preintervention Weight (Intervention Group)	Preintervention Weight (Comparison Group)	Follow-Up Time (Range)	Weight at Follow-Up (Intervention Group)	Weight at Follow-Up (Comparison Group)	Adverse Events or Withdrawal	Intervention Response	Risk of Bias
Lustig *et al.*, 1999 (141)	Nine patients, 11.1% CP (44.4% M)	Range, 3–14	Child	—	6-mo prestudy lifestyle intervention; octreotide (5 μg/kg/d divided into three doses, increased to maximum of 15 μg/kg/d)	Mean BMI, 36.0 kg/m^2 (SEM, 2.5) Mean weight, 103.1 kg (SEM, 11.2)	—	6-m intervention	6-m prestudy: ΔBMI, +2.1 (SEM, 0.3 kg/m^2) ΔWeight, +6.0 (SEM, 0.7 kg) Octreotide: ΔWeight, −4.8 (SEM, 1.8 kg) ΔBMI, −2.0 (SEM, 0.7 kg/m^2)	—	Abdominal discomfort, flatulence, and loose stools (n = 7), increased levothyroxine dose (n = 6), asymptomatic gallbladder sludging or small gallstones (n = 4), patient withdrew (n = 2), severe peripheral edema (n = 1), lack of weight loss (n = 1)	Weight loss (n = 5) or stabilization (n = 3) (responders), weight loss with continued therapy for 1 y (n = 2)	Very serious
Lustig *et al.*, 2003 (135)	10 Patients, 60% CP (60% M)	Unknown (childhood onset)	Child	10 patients; child, 70% CP; (50% M)	Octreotide or placebo (5 μg/kg/d divided into three doses, increased bimonthly to maximum of 15 μg/kg/d at 5 mo)	Mean BMI, 37.4 kg/m^2, (SEM, 2.5) Mean weight, 98.5 kg (SEM, 9.2)	Mean BMI, 36.8 kg/m^2 (SEM, 1.2) Mean weight, 102.7 kg (SEM, 6.8)	6-mo intervention	Mean BMI, 37.2 kg/m^2 (SEM, 2.5) Mean BMI change, −0.2 kg/m^2 (SEM, 0.2) Mean weight, 100.0 kg (SEM, 9.5) Mean weight change, +1.6 kg (SEM, 0.6)	Mean BMI, 39.0 kg/m^2 (SEM, 1.4) Mean BMI change, +2.2 kg/m^2 (SEM, 0.5) Mean weight, 111.9 kg (SEM, 7.5) Mean weight change, +9.1 kg (SEM, 1.7)	Treatment group: Abdominal discomfort and diarrhea (n = 9), cholesterol gallstone or sludge (n = 4), mild glucose intolerance (n = 2), patient withdrawal due to CP recurrence (n = 1) Placebo group: Diarrhea (n = 3), patient withdrawal due to diabetic hyperosmolar nonketotic coma (n = 1)	Significant weight stabilization in treatment group vs placebo group (responder information unreported)	Unclear
Jordaan *et al.*, 1996 (154)	One patient 0% CP (M)	33	Adult	—	Fluoxetine (20 mg daily for 1 wk and 60 mg daily thereafter) with switch to fenfluramine (60 mg daily)	Weight, 141 kg	—	3-mo intervention (fluoxetine), 6-wk intervention (fenfluramine)	Weight, 144 kg	—	None reported	No weight reduction (nonresponder)	Very serious

Table 3. Continued

First Author, Year of Publication	Population (Sex)	Age at CP Diagnosis (y)	Age of Cohort at Intervention	Comparison Population	Description of Intervention	Preintervention Weight (Intervention Group)	Preintervention Weight (Comparison Group)	Follow-Up Time (Range)	Weight at Follow-Up (Intervention Group)	Weight at Follow-Up (Comparison Group)	Adverse Events or Withdrawal	Intervention Response	Risk of Bias
Shoemaker *et al*, 2016 (136)	Eight patients with CP (37.5% M)	Unknown	Adult	Six patients, adult; 83.3% CP (33.3% M)	Beloranib or placebo (1.8 mg twice weekly)	Mean BMI, 43.4 kg/m^2 (SD, 8.0) Mean weight, 127.6 kg (SD, 22.8)	Mean BMI, 42.1 kg/m^2 (SD, 6.0) Mean weight, 124.8 kg (SD, 23.0)	4 wk with RCT	RCT	RCT	Treatment group: Dizziness (n = 2), headache (n = 2), nasopharyngitis (n = 2), reduced neutrophil count (n = 3), back pain (n = 1), mild diarrhea/viral gastroenteritis (n = 1)	Significant weight reduction in treatment group vs placebo group; all patients had (minor) weight reduction during beloranib treatment (responders)	Low
								4 wk open-label extension	Mean, −3.2 kg (95% CI, −5.4 to −0.9)	Mean, −0.3 kg (95% CI, unknown)	Placebo group: Headache (n = 2), nasopharyngitis (n = 1), patient withdrawal due to urticaria (n = 1)		
									Open label	Open label			
									Mean, −6.2 kg (95% CI, −8.2 to −4.1) compared with baseline	Mean, −3.0 kg (95% CI, −5.9 to −0.1) compared with initial open label			

Abbreviations: I, irradiation; IQR, interquartile range; S, surgery

Stimulants

Seven studies reported the effect of pharmacotherapeutic agents that increase metabolic rate or physical activity parameters (*i.e.*, stimulants). Two of these studies included dextroamphetamine as a stimulating agent.[138,146] In the first prospective study, the rate of monthly weight gain in five pediatric patients with CP significantly decreased from 2.0 kg/mo to 0.4 kg/mo after 24 months of intervention, with reported improvement in daily physical activity.[138] No significant differences were reported on parent-reported food intake. In the second retrospective chart review study, 12 adolescent patients received dextroamphetamine treatment.[146] Median weight decrease of the total cohort was −0.7 SDS in male patients and −0.44 SDS in female patients, after a median period of 13 months (range, 7 to 63 months). Subjective improvement in daytime wakefulness or exercise tolerance was reported in 11 of 12 patients. One case report indicated a decreased BMI with concomitant dose-dependent subjective decreased hunger after 87 weeks of methylphenidate treatment.[156] In another case report, weight decreased from 70 to 60 kg, and hyperphagia was abolished after mazindol administration for 3 weeks.[155] The positive effects on weight and hyperphagia remained stable for 3 years. In a retrospective case series, treatment with caffeine and ephedrine hydrochloride induced weight loss after 6 months of intervention.[166] However, weight gradually returned to baseline in one patient. Two studies evaluated the effect of supraphysiologic T3 administration on weight.[157,167] In the first retrospective study, weight loss was observed in all patients (n = 3) after an intervention period ranging between 11 and 27 months.[167] In the second study, BMI and BAT activity remained unchanged after 2 months of supraphysiologic T3 treatment in a pediatric patient with CP.[157]

We determined the number of responders and nonresponders from all seven studies. In total, 23 of 26 (88.5%) patients demonstrated either weight reduction or stabilization (responders) after treatment with stimulants. The percentage of responders was 88.2% (15 of 17) for dextroamphetamine, 100% (1 of 1) for methylphenidate, 100% for mazindol (1 of 1), 100% (3 of 3) for caffeine/ephedrine, and 75% (3 of 4) for supraphysiologic T3 supplementation. Adverse events during intervention with dextroamphetamine treatment included headache[138], enlargement of a CP cyst[138], insomnia[146], and tumor recurrence.[146] Shakiness was reported during caffeine and ephedrine treatment.[166] No adverse events were reported after intervention with methylphenidate, mazindol, or supraphysiologic T3.

Antidiabetic agents

Nine studies evaluated the effects of antidiabetic agents (*i.e.*, metformin, micronized fenofibrate, pioglitazone, diazoxide, GLP-1 agonists, or combinations) on weight. [137,139,140,142,148,158-160,165] In the first observational study, 10 of 22 patients did not experience weight loss after a lifestyle intervention and started treatment with metformin and micronized fenofibrate.[140] After 6 months, no significant weight change was reported for these patients, although HOMA-IR significantly

decreased. In one case report, the insulin sensitizers pioglitazone and metformin did not induce weight loss in a female patient with type 2 diabetes mellitus (T2DM), although variations in weight and symptoms of hyperphagia were reported.[165] The agents did improve glycemic control (reduced HOMA-IR and HbA1c). A prospective study evaluated the combination of diazoxide and metformin therapy in nine adolescent patients with CP.[139] In the seven patients who completed the study, BMI was significantly reduced (–0.3 kg/m^2/6 mo) during the intervention period, as compared with that of the prestudy period with lifestyle intervention alone (+2.2 kg/m^2/6 mo, $P = 0.02$). Weight loss occurred primarily in patients who had the highest levels of insulin secretion at the start of the intervention. In a RCT including 35 pediatric patients treated with either diazoxide (n = 18) or placebo (n = 17) for 6 months, BMI was not significantly altered between the treatment group or the placebo group.[137]

Five studies used GLP-1 agonists, with sample sizes ranging from one to 10 adult patients. [142,148,158-160] In three case reports, treatment with GLP-1 agonists (exenatide, liraglutide, or dulaglutide) reduced weight in all patients after a follow-up ranging between 2 months and 4 years.[158-160] A large retrospective study described exenatide or liraglutide treatment of 24.3 months (range, 6 to 51 months) in nine adult patients, of whom eight suffered from T2DM.[148] All eight patients who completed the study lost weight and experienced reduced BMIs from 37.6 kg/m^2 to 33.4 kg/m^2 ($P < 0.01$). A second large study consisted of a prospective open-label intervention study, including 10 patients who received exenatide for 50 weeks.[142] Of the eight patients who completed the study, six lost weight (mean, –3.3 kg; range, –6.2 to –0.2 kg), but overall weight loss was not significant.

The use of GLP-1 agonists reduced appetite and cravings for food and increased feelings of satiety after food ingestion in all studies. In one study, the patients who reported decreased food intake had accompanying weight loss, whereas two patients who gained weight also reported increased food intake.[142] Of five studies of GLP-1 agonist interventions, two included patients with well-controlled T2DM or HbA1c levels <7%.[136,158] The case report noted significant weight loss; however, HbA1c concentrations remained constant.[158] No weight loss occurred after GLP-1 use in the prospective study, and HbA1c concentrations at follow-up were unreported.[142] Three studies reported decreased HbA1c concentrations and significant weight loss after GLP-1 agonist use.[148,159,160] The numbers of responders vs nonresponders were retrieved in seven of nine studies. In total, 20 of 32 (62.5%) patients experienced either weight reduction or stabilization (responders) after treatment with antidiabetics. The percentage of responders was 0.0% (0 of 1) for pioglitazone combined with metformin, 33.3% (3 of 9) for diazoxide combined with metformin, and 77.3% (17 of 22) for GLP-1 agonists. Adverse effects reported during treatment with GLP-1 agonists included nausea and/or vomiting[142,148,159], joint pain[142], irritability and mood swings[142], injection site reactions[142], and kidney stones[142]. Mildly elevated hepatic enzymes,

vomiting[139], and pedal edema[139] were reported during combined treatment with diazoxide and metformin. Decreased urinary volume and edema[137], diabetes mellitus[137], and hirsutism[137] occurred during diazoxide monotherapy. No adverse events were reported after interventions with combined metformin and micronized fenofibrate or pioglitazone and metformin.

Hypothalamic-pituitary substitution therapy

Two large retrospective cohort studies evaluated the effect of GH treatment on BMI in patients with GH deficiency and CP.[147,151] GH treatment increased height and weight in a pediatric cohort (n = 199), and BMI remained stable after 3 years of GH treatment. During GH treatment of 5 years, weight significantly increased in an adult cohort (n = 260) comprising patients with CP, although waist circumference and fat mass remained unchanged.[151] In both studies, the numbers of responders or nonresponders could not be retrieved, and neither study reported adverse outcomes during GH treatment.

Other agents

Two studies reported the effects of octreotide (a somatostatin analog) on weight.[135,141] An uncontrolled prospective study with nine pediatric patients reported significantly reduced mean BMI after 6 months (-2.0 ± 0.7 kg/m^2), as compared with a 6-month prestudy lifestyle intervention (+2.1 ± 0.3 kg/m^2, $P = 0.0001$).[141] A follow-up RCT demonstrated weight stabilization in the treatment group after 6 months. In both studies, insulin response decreased by the end of the intervention period. The numbers of responders vs nonresponders were reported in only the uncontrolled study. In total, eight of nine (88.8%) patients experienced either weight loss or weight stabilization after octreotide therapy. Importantly, note that octreotide is currently not approved by the Food and Drug Administration (FDA) or the European Medicines Agency (EMA) for HO treatment and is not recommended as intervention for weight management. Adverse events reported during octreotide treatment included CP recurrence[135], abdominal discomfort and diarrhea[135,141], adjustments of T4 supplementation dose[141], cholesterol gallstone or sludge formation[135,141], peripheral edema[141], mild glucose intolerance[135], and diabetic hyperosmolar nonketotic coma.[135]

The effects of the selective serotonin reuptake inhibitors fluoxetine and fenfluramine were evaluated in one case report.[154] No beneficial effect on weight, sleep-wake cycles, or eating behaviors was reported (nonresponder). A recent double-blind, placebo-controlled phase 2a clinical study allocated 14 adult patients to either a treatment arm with the MetAP2 inhibitor beloranib (n = 8) or a placebo arm (n = 6) for an intervention period of 4 weeks.[136] After 4 weeks, the study was extended into an open-label study, during which all patients received beloranib. In the treatment group, significant weight loss was observed at week 4 and week 8 (–6.2 kg after 8 weeks, compared with baseline). In the placebo group, weight loss occurred only in the extended open-label period (–3.0 kg after 4 weeks). Decreased food intake was reported only during the

open-label period in both the treatment (–37%; 95% CI, –53%, –21%) and placebo groups (–54%; 95% CI, –79%, –29%). All patients demonstrated weight reduction during beloranib treatment (responders). Among all adverse events during beloranib treatment, the most frequent and/or severe were urticaria, dizziness, headache, back pain, nasopharyngitis, mild diarrhea/viral gastroenteritis, sleep disturbances, and neutropenia/reduced neutrophil counts.[136]

Surgical interventions

Bariatric surgery

Ten studies reported weight outcomes after bariatric surgery in 39 patients[149,150,161,162,168-173] (Table 4). LAGB was performed in six children and 4 adults; SG was performed in one child and 10 adults; and gastric bypass (or biliopancreatic derivation with duodenal switch in one case) was performed in four children and 14 adults. In a retrospective study including four patients with CP (aged 13.8 to 23.7 years) who underwent LAGB, weight loss was observed after a short follow-up period, but not after long-term follow-up periods (5.3 to 9.1 years), despite noted changes in eating behavior initially.[169] In a retrospective case series, weight was reduced in all three patients (aged 21 to 24 years) after SG during a follow-up time of 2 years.[173] However, in one patient, continuous weight regain occurred after the first 6 months. Four small case reports/series reported weight loss in all eight patients after gastric bypass surgery (follow-up period between 19 and 65 months).[161,162,168,172] However, one patient demonstrated a pattern of weight regain.[172] In one of these case reports, significantly reduced cravings for fats, sweets, carbohydrates, and fast food were noted.[161]

Four studies reported weight parameters after different bariatric surgical modalities. In the first retrospective case series, BMI decreased in two patients (aged 24 and 43 years) after SG and in one patient after gastric bypass surgery (aged 51 years), with a follow-up period ranging between 30 and 48 months.[170] One patient experienced a BMI increase from 37.7 kg/m^2 at the time of gastric bypass surgery to 49 kg/m^2 at 64 months after surgery. In a prospective case series, three patients with CP (aged 18 to 48 years) experienced weight loss after either Roux-en-Y gastric bypass (RYGB) (n = 2) or SG (n = 1), after a follow-up period of 18 months. All three patients had decreased food intake after the first postoperative month; however, this returned to preoperative food amounts by 1 year postsurgery.[171] A larger retrospective study included nine patients with CP (median age, 17.0 years; range, 12 to 30 years) who underwent LAGB (n = 6), SG (n = 4), and/or gastric bypass (n = 2).[149] after LAGB. Two patients received SG after initial LAGB surgery, and one patient underwent gastric bypass after LAGB. After a median follow-up period of 5.5 years and 2 years, respectively, no weight change occurred after LAGB or SG. In contrast, the two patients who underwent gastric bypass surgery experienced weight loss after a mean follow-up period of 3 years. A control group who underwent bariatric surgery for "common" obesity experienced significant weight loss after all three different surgical procedures.

A recent retrospective study included eight adult patients with CP who were matched to a group of 75 patients from the general population.[150] After RYGB (n = 6, aged 32.6 ± 17.3 years), mean weight loss was similar to that of the control population (–25% vs –29%, $P = 0.419$), whereas mean weight loss was significantly reduced after SG (n = 2, aged 34.7 ± 7 years) than in the control population (–10% vs –20%, $P = 0.003$) after 2 years of follow-up. Pre-existing T2DM resolved during the follow-up period for three patients who underwent SG and in one patient who underwent gastric bypass.[150,173] Decreased fasting insulin and/or HbA1c concentrations and/or HOMA-IR were also reported in three studies.[162,171,172]

The numbers of responders vs nonresponders were partially reported in nine of 10 studies. In total, 19 of 24 (79.2%) patients experienced weight loss after bariatric surgery. The percentage of responders was 0.0% (0 of 4) for LAGB, 100.0% (6 of 6) for SG, and 92.9% (13 of 14) for gastric bypass. However, two patients regained weight after either SG or RYGB. Postoperative complications included mild iron-deficiency anemia after RYGB[161]; mild folic acid and vitamin D deficiency[173], minor bleeding[173], impaired effectiveness of oral desmopressin[149], and vomiting[149] after SG; and abdominal pain, dysphagia, vomiting (in one patient due to adrenal crisis)[149], banding readjustment[149], and device explantation[149] after LAGB. Reflux[149] was also reported but was not specified after which surgical intervention. One female patient developed diarrhea, abdominal pain, and later dumping syndrome after RYGB.[168] She also suffered from excessive tiredness, multifocal pains, and hyperuricemia and required cholecystectomy for acute gallstone pancreatitis. Another patient developed *Klebsiella* septicemia, esophagus ulcerations, and diabetes insipidus crisis after gastric bypass.[170] A third patient required pacemaker implantation after sustained tachycardia and two laparoscopic surgical repairs after bariatric surgery (biliopancreatic derivation with duodenal switch) for inflammatory intestinal stenosis.[168]

Other surgical interventions

Truncal vagotomy decreased weight (–30 kg) and fasting insulin levels and improved feelings of satiety after 27 months of follow-up in a 19-year-old female patient (responder).[163] The patient reported occasional foul-smelling eructations due to prolonged retention of gastric contents as an adverse effect. In another 19-year-old female, the implantation of DBS electrodes to bilaterally stimulate the nucleus accumbens resulted in decreased weight (–13 kg) and improved symptoms of hyperphagia after a follow-up period of 14 months (responder).[164] No adverse events occurred, although the efficiency of executive functions was marginally decreased shortly after the surgery, but later improved to a near presurgical level.

Table 4. Descriptive characteristics of studies with surgical interventions

First Author, Year of Publication	Population (Sex)	Age at CP Diagnosis (y)	Age of Cohort at Intervention	Comparison Population	Description of Intervention	Preintervention Weight (Intervention Group)	Preintervention Weight (Comparison Group)	Follow-Up Time (Range)	Weight at Follow-Up (Intervention Group)	Weight at Follow-Up (Comparison Group)	Adverse Events or Withdrawal	Intervention Response	Risk of Bias
Müller *et al.*, 2011 (169)	Four patients with CP (25% M)	Range, 2–20	Child, adult	—	LAGB	BMI, 46.4 kg/m^2, 44.9 kg/m^2, 51.9 kg/m^2, 40.0 kg/m^2 BMI SDS, 10.9, 10.4, 11.4, 6.2	—	Median, 7.1 y (range, 5.3–9.1)	BMI, 49.6 kg/m^2, 53.6 kg/m^2, 53.6 kg/m^2, 42.7 kg/m^2 BMI SDS, 10.2, 13.9, 10.2, 6.3	—	None reported	No long-term BMI reduction (nonresponders)	Very serious
Trotta *et al.*, 2017 (173)	Three patients with CP (33.3% M)	Range, 6–16	Adult	—	SG	Mean BMI, 49.2 kg/m^2 (range, 41.6–58.1) Weight: 112 kg, 180 kg, 153 kg	—	2 y	Mean BMI, 35.3 kg/m^2 (range, 31.2–40.6) Weight loss, 25.0%, 41.1%, 17.6%	—	Minor bleeding (n = 1), mild folic acid and vitamin D deficiency (n = unknown)	Weight reduction in total cohort (responders), weight regain after 6 mo (n = 1)	Very serious
Inge *et al.*, 2007 (161)	One patient with CP (M)	14	Adult	—	RYGB with truncal anterior vagotomy	BMI, 67 kg/m^2 Weight, 223.5kg	—	2.5 y	Weight loss, 49 kg	—	Mild iron-deficiency anemia	Weight reduction (responder)	Very serious
Page-Wilson *et al.*, 2012 (162)	One patient with CP (F)	16.5	Adult	—	RYGB	BMI, 51.6 kg/m^2 Weight 128.2 kg	—	9 mo	BMI 39.0 kg/m^2 Weight, 93.9 kg	—	None reported	BMI reduction (responder), stable weight 19 mo after intervention	Very serious
Rottembourg *et al.*, 2009 (168)	Two patients with CP (50% M)	Range, 4–6	Child	—	RYGB (n = 1), bariatric surgery by biliopancreatic derivation with duodenal switch (n = 1)	BMI, 65 kg/m^2, 45 kg/m^2 Weight, 135 kg, 133 kg	—	4 and 2 y	BMI, 43 kg/m^2, 32 kg/m^2	—	Diarrhea, chronic pain, fatigue, dumping-type syndrome, and psychologic deterioration (n = 1); bradycardia necessitating a pacemaker and intestinal stenosis requiring laparoscopic surgical repairs (n = 1)	BMI reduction (responders)	Very serious
Wolf *et al.*, 2016 (172)	Four patients with CP (25% M)	Unknown	Child, adult	—	Gastric bypass surgery	BMI, 49.2 kg/m^2, 59.5 kg/m^2, 41.0 kg/m^2, 46.1 kg/m^2 Body weight, 174 kg, 170 kg, 120 kg, 112 kg	—	Range, 13–65 mo (33, 65, 17, and 13 mo, respectively)	BMI, 29.4 kg/m^2, 53.6 kg/m^2, 32.5 kg/m^2, 28.7 kg/m^2 Body weight, 104 kg, 153 kg, 95 kg, 70 kg	—	None reported	BMI reduction in all (responders) Weight regain suggested in one	Very serious

Table 4. Continued

First Author, Year of Publication	Population (Sex)	Age at CP Diagnosis (y)	Age of Cohort at Intervention	Comparison Population	Description of Intervention	Preintervention Weight (Intervention Group)	Preintervention Weight (Comparison Group)	Follow-Up Time (Range)	Weight at Follow-Up (Intervention Group)	Weight at Follow-Up (Comparison Group)	Adverse Events or Withdrawal	Intervention Response	Risk of Bias
Catta *et al.*, 2013 (170)	Four patients, 75% CP (50% M)	Range, 12–47	Adult	—	SG (n = 2), gastric bypass surgery (n = 2)	SG: BMI, 51 kg/m^2, 37.6 kg/m^2	—	SG: 30 mo	SG: BMI, 41 kg/m^2, 34 kg/m^2	—	*Klebsiella* septicemia, esophagus ulcerations, and diabetes insipidus crisis (n = 1)	BMI reduction (n = 3) (responders), BMI increase (n = 1) (nonresponder)	Very serious
						Gastric bypass: 43.7 kg/m^2, 37.7 kg/m^2		Gastric bypass: 48 and 64 months	Gastric bypass: 37.5 kg/m^2, 49 kg/m^2				
Bretault *et al.*, 2016 (171)	Three patients with CP (66.6% M)	Range, 8–41	Adult	—	RYGB (n = 2), SG (n = 1)	BMI, 47.2 kg/m^2, 59.6 kg/m^2, 42.3 kg/m^2	—	18 mo	Mean weight change, −20 kg	—	No adverse events after surgery	Weight reduction (responders)	Very serious
						Weight, 127 kg, 189 kg, 148 kg			Net weight loss, −9%, −19%, −9%				
Weismann *et al.*, 2013 (149)	Nine patients with CP (22% M)	Median, 10 (range, 1–21)	Child, adult	General population: LAGB (n = 40), SG (n = 49), gastric bypass (n = 54) Adult: % male unknown	LAGB (n = 6), followed by SG (n = 2) or gastric bypass surgery (n = 1); SG (n = 2); gastric bypass surgery (n = 1)	LAGB: BMI, 44.7 kg/m^2, 44.7 kg/m^2, 52.1 kg/m^2, 40.2 kg/m^2, 44.5 kg/m^2, 61.6 kg/m^2 Weight, 150 kg, 145 kg, 122 kg, 98 kg, 127 kg, 176 kg	Unknown	LAGB: Median, 5.5 y (range, 1–9)	LAGB: No difference in weight change or BMI	LAGB: Weight loss, 14.7% (SD, 4)	LAGB: Abdominal pain, dysphagia, vomiting, and reflux (n = unknown),	No weight reduction after LAGB or SG; weight reduction after RYGB (n = 2) (responders); weight loss after all three procedures in comparison group	Serious
						SG: BMI, 55.6 kg/m^2, 43.3 kg/m^2 Weight, 160 kg, 132 kg		LAGB control: Median, 3 y (range, 1–7)	SG: No difference in weight change or BMI	SG: Weight loss, 33% (SD, 3.8)	band readjustment (n = 2), device explantation (n = 4), adrenal crisis (n = 1)		
						Gastric bypass: BMI, 48.6 kg/m^2 Weight, 152 kg		SG: Mean, 2 y (range, 0.5–4)	Gastric bypass: Loss of body weight	Gastric bypass: Weight loss, 38% (SD, 9)	SG: Vomiting and impaired effectiveness of oral desmopressin (n = 1)		
								SG control: Mean, 1 y (range, 0.5–6)					
								Gastric bypass: Mean, 3 y (range, 2–4)					
								Gastric bypass control: Mean, 2 y (range, 0.5–5)					

Table 4. Continued

First Author, Year of Publication	Population (Sex)	Age at CP Diagnosis (y)	Age of Cohort at Intervention	Comparison Population	Description of Intervention	Preintervention Weight (Intervention Group)	Preintervention Weight (Comparison Group)	Follow-Up Time (Range)	Weight at Follow-Up (Intervention Group)	Weight at Follow-Up (Comparison Group)	Adverse Events or Withdrawal	Intervention Response	Risk of Bias
Wijnen *et al.*, 2017 (150)	Eight patients with CP (12.5% M)	Range, 6–48	Adult	General population: RYGB (n = 45), SG (n = 30) Adult (12% M)	RYGB (n = 5), SG (n = 3), followed by RYGB surgery (n = 1)	Total group: Mean BMI, 43.3 kg/m^2 (SD, 4.1)	Total group: Mean BMI, 40.3 kg/m^2 (SD, 4.4)	2 y	Total group: Mean weight loss, 19%	Total group: Mean weight loss, 25%	Unable to report perioperative and postoperative complications of bariatric surgery	Weight loss in intervention and comparison groups after SG; weight loss in intervention and comparison groups after RYGB (responder information unreported)	Serious
						RYGB: Mean BMI, 43.4 kg/m^2 (SD, 5.2)	RYGB: Mean BMI, 40.1 kg/m^2 (SD, 3.6)		RYGB: Mean weight loss, 25%	RYGB: Mean weight loss, 29%			
						SG: Mean BMI, 43.1 kg/m^2 (SD, 1.9)	SG: Mean BMI, 40.4 kg/m^2 (SD, 4.9)		SG: Mean weight loss, 10%	SG: Mean weight loss, 20%			
Smith *et al.*, 1983 (163)	One patient with CP (F)	12.5	Adult	—	Truncal vagotomy	Weight, 106 kg	—	27 mo	Weight, 76 kg	—	Occasional foul-smelling eructations due to prolonged retention of gastric contents	Weight reduction (responder)	Very serious
Harat *et al.*, 2013 (164)	One patient with CP (F)	Unknown (childhood onset)	Adult	—	Bilateral implantation of DBS electrode to nucleus accumbens	BMI, 52.9 kg/m^2 Weight, 151.4 kg	–	14 mo	BMI, 48.3 kg/m^2 Weight, 138 kg	—	No side effects of treatment	BMI reduction (responder)	Very serious

Discussion and development of an individualized treatment algorithm

The increased morbidity and reduced QoL associated with severe, progressive HO is one of the most disrupting consequences after treatment of CP or other suprasellar tumors. Despite high-quality recommendations for treatment of obesity in children and adults in the general population, these recommendations can only be partially applied for management of HO after CP and other suprasellar tumors. Barriers to start an intervention should be lower in patients with CP or other suprasellar tumors because a variety of correlated clinical symptoms cause rapidly progressive weight gain. The combination of decreased satiety and reduced energy expenditure requires lifelong compliance with dietary and behavioral modifications, including regular physical activity. Because many patients with CP also suffer from food cravings and behavioral disorders, lifelong dietary compliance is not easily achievable. Therefore, additional HO interventions are urgently needed. High-quality studies aiming at HO interventions for patients with CP and other suprasellar tumors are rare and yield, on average, modest results. However, when specific subgroups of patients are identified within these studies, beneficial effects may be elucidated (*i.e.*, responders vs nonresponders). By combining these effects in subgroups of patients, together with the identification of specific clinical symptoms based upon the underlying pathophysiologic causes for obesity, targets for individual interventions may be identified. In the following sections, we propose an individualized treatment algorithm, with a stepwise approach for each clinical domain, by combining our current understanding of the pathophysiologic underpinnings of CP-associated HO with our findings from the systematic review of relevant studies (Fig. 3).

A. Psychosocial disorders

Assessment of psychosocial disorders

In all patients with CP and other suprasellar tumors, professional health care providers should carefully perform psychosocial assessments. Several validated questionnaires are available to determine whether psychosocial disorders are present, although they are mainly used for research purposes. The Brief Symptom Inventory–18 measures psychologic distress by using 18 items related to symptoms experienced during the previous 7 days. The Medical Outcomes Short Form–36 assesses domains of general health, well-being, and QoL during the previous 4 weeks.[174] For patients with GH deficiency, a specific questionnaire consisting of 25 items that evoke yes/no answers, acknowledging or denying certain issues, is available.[175] In pediatric patients, the Pediatric Quality of Life questionnaire may be applied. More well-validated questionnaires used to assess neurobehavioral, social, and emotional dysfunction in patients with CP are included in a review by Zada *et al.*[75]

Interventions targeting psychosocial disorders

In one of the two studies that assessed the effect of visiting a specialized outpatient clinic, a substantial proportion of patients (45.5%) had no weight gain (responders).[144] This emphasizes that multidisciplinary treatment in a specialized neuroendocrinology clinic may be beneficial for weight in a subset of patients. This should be the first step of HO management for all patients with CP or other suprasellar tumors (weak recommendation, clinical evidence). As severe weight gain mainly occurs in the first 6 months after tumor resection, counseling of patients (and their parents) about potential changes in eating behaviors, reduced metabolic state, and the increased need for active lifestyles should occur preoperatively. Involving the social environment (*e.g.*, family, school, and sport clubs) in HO management is also important.[80,152] Because of possible adverse psychologic effects on children when they are isolated from their social environment, together with lack of long-term benefits, we discourage hospitalization specifically targeting weight loss (weak recommendation, clinical evidence). Hospitalization may be used for diagnostics, for example, to identify barriers to compliance with healthy life styles or to illustrate the effect of dietary interventions when strictly pursued. In the rehabilitation setting reported by Sterkenburg *et al*., no beneficial effects on weight were found.[145] However, as the BMIs in the rehabilitation group were significantly higher than those of the control population and changes in BMI were not analyzed, the potential beneficial effects of rehabilitation on HO remain unclear.

Management of specific psychosocial and/or psychiatric disorders, such as impulse-control disorders, depression, anxiety, and severe food craving behaviors requires additional psychosocial and psychiatric support (recommendation, expert opinion).[176] Pharmacotherapeutic options may also be beneficial for psychosocial and/or psychiatric disorders in pediatric and adult patients with CP or other suprasellar tumors. Dextroamphetamines improve hyperactivity and concentration and may be considered to target psychosocial symptoms (weak recommendation, clinical evidence).[138,146] Methylphenidate may alleviate concentration disorders, although this outcome was not reported.[156] Of note, two case reports that were not included in our systematic analysis because of ineligible formats reported positive responses in patients with CP to topiramate for treatment of impulse-control disorders.[177,178]

Recommendations to target psychosocial disorders

- Both children and adults with CP or other suprasellar tumors with HO should visit specialized outpatient clinics (weak recommendation).
- Hospitalization should be discouraged for children with CP or other suprasellar tumors with HO, as rapid weight regain occurs after discharge (weak recommendation).

- Additional psychosocial and psychiatric support may be required to manage specific psychosocial and/or psychiatric disorders of children and adults with CP or other suprasellar tumors and HO (expert opinion).
- Dextroamphetamine may be considered for children and adults with CP or other suprasellar tumors with HO and psychosocial disorders (weak recommendation).

Future interventions for psychosocial disorders

Centralizing care for patients with CP and other suprasellar tumors and HO will improve the quality of care in neuroendocrinology clinics. Funding to support healthy dietary and exercise habits in the home environment should be actively sought. Studies that focus on improving neurocognitive and social behavior are needed. Because symptoms such as attention and/or concentration impairment or sleep disturbances are also found in patients with acquired brain injury (ABI), findings from ABI studies should be integrated into CP care.[179,180] Understanding the mechanisms that contribute to psychosocial, psychologic, and psychiatric disorders, irrespective of direct hypothalamic damage, and the interventions used for patients with ABI may improve psychosocial disorders in patients with CP-associated HO.

A promising agent that may potentially influence behavior in patients with CP is oxytocin. Oxytocin is associated with social attachment and influences social relationships.[181] In healthy individuals, oxytocin increases trust, social cognition, and empathy.[182,183] For these reasons, oxytocin has gained recent interest to use in patients with autism spectrum disorders.[184,185] In patients with Prader-Willi syndrome, studies report beneficial effects on social and emotional behavior after oxytocin administration, however important study limitations exist.[186] Although defects in oxytocin secretion by the PVN and supraoptic hypothalamic nuclei are not universally found in CP, exogenous oxytocin treatment does improve social behaviors, such as emotion perception.[83,84] A recent case report described weight loss as a primary outcome after combined oxytocin/naltrexone administration in a patient with CP and HO (discussed below).[187]

B. Hyperphagia

Assessment of hyperphagia

The presence of hyperphagia can be first assessed by the presence of overeating, that is, increased food intake relative to personal need. However, objectively assessing food intake is challenging. Several validated questionnaires to measure food intake are available. In general, three distinct methodologies exist: food records, 24-hour recall, and food frequency questionnaires.[188] A limitation of such questionnaires is that food intake is often underreported, especially by obese subjects or those who want to lose weight. Factors such as age, female sex, and demographic and psychologic factors also influence underreporting of food intake.[189,190] Because assessment of food intake is not standardized and depends on the different objectives (*i.e.* amount, frequency

or type of food intake), questionnaire choice should be tailored for individual patients.[191] Food records and food frequency questionnaires are the most cost-effective approaches but require compliance. The 24-hour recall methodology is fairly reliable because it only requires short-term memory, but differences in day-to-day intake may go unnoticed. Food intake is best measured when people have free access to food, but this may be difficult and unethical in patients with CP, especially in children or patients with learning and behavioral difficulties. Lack or short duration of satiety, preoccupation with food, and food-seeking behaviors are also signs of hyperphagia.[192] Special assessment tools, derived primarily from Prader-Willi research can be used to assess (changes in) eating behavior and hyperphagia symptoms.[193-195]

Interventions targeting hyperphagia

Guidelines that address obesity in the general population recommend combined intensive lifestyle interventions, including dietary, physical activity, and behavioral support for both children and adults (recommendation, existing guidelines).[196-198] Although numerous weight loss programs specifically target carbohydrate or fat levels, a recent meta-analysis showed that different diets produced similar effects on obesity in the general population.[199] In patients with CP and hypopituitarism, the risk of hypoglycemia from adrenal crisis should be considered when recommending a high-protein, low-carbohydrate diet. Nevertheless, recommending dietary plans that patients will likely adhere to is advisable because of the need for lifelong compliance. For patients with impulse-control disorders, combined with extreme food craving behaviors, specific psychosocial and psychiatric support may be offered to the patient (and/or parents) (recommendation, expert opinion).

Pharmacotherapeutic interventions for attention-deficit disorders may also decrease hyperphagia. Stimulants such as dextroamphetamine may affect hyperphagia by inhibiting reuptake of dopamine, norepinephrine, and/or serotonin and thereby cause anorexia.[200] Methylphenidate may elicit a food reward response and suppress the drive to eat.[201] Other agents, such as mazindol and ephedrine, suppress food intake by direct stimulation of β-adrenergic receptors and inhibit the feeding center of the LHA.[202] Only methylphenidate and mazindol, which is currently not FDA and EMA approved for obesity or behavioral disorders, demonstrated decreased hyperphagia in the reviewed studies (weak recommendation, clinical evidence).[155,156] Although the clinical evidence to recommend methylphenidate is very limited, this agent has been demonstrated to reduce binge eating in patients with attention-deficit/hyperactivity disorder, and may be beneficial in patients with CP (support of weak recommendation by expert opinion).[203,204]

Recommendations for the use of stimulants in children with obesity in the general population are discouraged because of drug-associated adverse effects, the addictive properties of such drugs, and an absence of trials demonstrating long-term weight loss efficacy.[196] Importantly,

also note that none of these stimulating agents has been approved for the treatment of obesity in children. In adults, the FDA-approved and recommended norephinephrine-releasing agents for obesity are phentermine (short-term use), diethylpropion (short-term use), and combination therapy with phentermine/topiramate (long-term use).[197,205,206] However, the EMA has not approved phentermine/topiramate because of cardiac, psychiatric, and teratogenicity risks. Lisdexamfetamine dimesylate has only been approved for the indication binge eating in adults, and attention-deficit/hyperactivity disorder in patients >6 years of age.[207] In patients with CP, consideration of whether adverse effects, such as addiction, insomnia, increased heart rate, dry mouth, and constipation, outweigh the potential benefits on hyperphagia and weight loss should be made for each patient individually.

The incretin GLP-1 is closely involved in the process of insulin secretion, delays gastric emptying, and can bind to receptors in the hypothalamus and hindbrain, enhancing the perception of satiety.[208] All five studies that assessed the effects of GLP-1 agonists reported improved hyperphagia symptoms and weight loss in most patients (weak recommendation, clinical evidence). None of these studies included pediatric CP patients. Currently, GLP-1 agonists have been approved only for T2DM management in adults, except for liraglutide, which is approved for long-term treatment of overweight in obese adults.

The serotonergic system is also involved in satiety feeling via three different neurons with serotonin receptors: POMC neurons, NPY/AgRP neurons, and brainstem neurons.[209-211] Activation or inhibition of these neurons by serotonergic agents improve within-meal satiation and postmeal satiety processes, which reduces total food intake. In the only study evaluating serotonergic agents, both fenfluramine and fluoxetine did not induce weight loss or alterations in eating behavior.[154] The serotonin/noradrenalin reuptake inhibitor sibutramine was evaluated in a double-blind RCT for beneficial effects on weight, but because most patients suffered from HO due to nonacquired causes (Prader-Willi syndrome or Laurence-Moon-Bardet-Biedle syndrome), this study was excluded from the systematic analysis.[212] However, in this patient group, significant weight loss occurred after sibutramine administration, although this effect was more pronounced in children without HO. Of note, several serotonergic agents have been withdrawn from the European and/or US drug market because of serious adverse effects, such as valvular heart disease, pulmonary hypertension, and psychiatric disorders.[213]

MetAP2 inhibitors comprise a new class of antiobesity agents, of which the mechanism of action is not yet totally understood. Originally, MetAP2 inhibitors were suggested as anticancer therapy by potential inhibition of MetAP2, an enzyme involved in vascular endothelial growth factor expression and angiogenesis. MetAP2 inhibition results additionally in downregulation of the lipid synthesis pathway in the liver and adipose tissue and stimulation of fatty acid catabolism.[214] The included study assessed the effect of beloranib in patients with CP and reported a decreased

food intake and weight loss.[136] This may have resulted from improved leptin sensitivity or an unknown central acting effect.[215] Clinical research with beloranib was recently halted because of two fatal events of pulmonary embolism and two events of deep vein thrombosis in a phase 3 study including patients with Prader-Willi syndrome.[216] Besides these very serious adverse effects on venous thrombotic events in clinical studies, the immunosuppressing effect and reported psychiatric adverse events (*e.g.*, aggression and anxiety) associated with beloranib are of additional concern.[216] Although the FDA has placed beloranib on clinical hold, new MetAP2 inhibitors are currently being developed and tested in phase 1 clinical trials.[217]

Bariatric surgery has been suggested to reduce food intake by changes in food choice, taste, hedonic evaluation, motivation, and self-control, although the exact mechanisms that affect the gut-brain axis are not exactly known.[218] Positive effects of bariatric surgery on eating behavior were reported in three studies, although its long-term effect may be questioned.[161,169,171] In the included studies, successful weight loss occurred only after SG and RYGB and not after LAGB. Two recent meta-analyses support that weight regain occurs after LAGB, but also after SG in patients with CP within 1 year after surgery.[150,219] Additionally, the reported maximum weight loss after 1 year seems significantly less than in patients with obesity in the general population.[219,220] Differences in weight loss after various surgical procedures in patients with CP may be attributed to gut hormones (especially GLP-1). After bariatric surgeries, a significant rise in GLP-1 concentrations occurs, which is much higher after RYGB than after restrictive procedures.[221] The hypothesis that increasing GLP-1 levels will lead to weight loss was clinically assessed in three patients with CP.[162,171] Increased GLP-1 levels occurred after RYGB but not after SG.

Hypopituitarism frequently occurs in patients with CP who have undergone bariatric surgery, and differences in oral fluid intake, nausea, vomiting, and malabsorption can severely affect the bioavailability of drugs. However, in only two of eight studies that reported hormone replacement therapy after surgery, impaired effectiveness of desmopressin or fluctuation in postoperative desmopressin administration occurred after SG.[149,173] In one patient, oral desmopressin was transitioned to nasal desmopressin preoperatively for RYGB to prevent delayed onset of action with oral administration.[162] Only one study reported an adrenal crisis after LAGB implantation.[149] It is important that pituitary dysfunction, especially diabetes insipidus and central adrenal insufficiency, are adequately treated and well controlled before bariatric surgery. During the long-term follow-up period, minimal or no changes in endocrine supplementation management were necessary to maintain adequate hormone levels in patients with CP.[150,172,173] However, other serious complications after bariatric surgical interventions may occur (see adverse effects) and must be considered.

In pediatric patients with CP, experience with bariatric surgery is limited, although all three procedures have been applied in this population. In the current guideline for pediatric obesity,

only morbidly obese children with advanced puberty who have obtained near final or final height and who demonstrate the ability to adhere to the principles of healthy dietary and activity habits may be considered for bariatric surgery.[196] The decision for bariatric surgery should be made on an individual basis, as the beneficial (long-term) effects and risks for adverse effects may vary (weak recommendation, clinical evidence). Other surgical interventions resulting in weight loss included truncal vagotomy and DBS of the nucleus accumbens.[163,164] Truncal vagotomy relies on interruption of the vagus nerve in gut-brain communication and improves feelings of fullness and satiety. DBS can target food reward systems by modulating dopamine release and modifying the hedonic value given to food.[222] Although both studies reported normalized appetites, these interventions should be considered as highly experimental and are currently not recommended as interventions for HO.

Recommendations to target hyperphagia

- Combined lifestyle interventions, including diet, should always be included for children and adults with HO and hyperphagia after treatment of CP or other suprasellar tumors (existing guidelines[196-198]).
- Additional psychosocial and psychiatric support may be required to manage impulse-control disorders, combined with extreme food craving behaviors of children and adults with CP or other suprasellar tumors and HO (expert opinion).
- Methylphenidate may be considered for children with HO and hyperphagia after treatment of CP or other suprasellar tumors (weak recommendation, supported by expert opinion).
- GLP-1 agonists may be considered for adults with HO and hyperphagia after treatment of CP or other suprasellar tumors. In case they have not been FDA or EMA approved for the indication obesity, they should only be considered in the context of an ethically approved research study (weak recommendation).
- Bariatric surgical procedures may be considered for adults with morbid HO and hyperphagia after treatment of CP or other suprasellar tumors (weak recommendation).

Future interventions for hyperphagia

Attempts have been made to quantify hypothalamic damage in patients with CP by using MRI of distinct brain sections to identify various hypothalamic nuclei.[223] Although such strategies may be promising, the reliability of assessments made from them may be improved in the future by advanced MRI techniques (*e.g.*, use of specific sequences or 7-T MRI scanners) or functional MRI that visualizes active brain regions according to blood oxygenation or the use of specific tracers.[224,225]

Pharmacotherapeutic options may depend on the precise damage caused by the tumor. For example, if arcuate nucleus neurons (including POMC- and AgRP/NPY-expressing neurons) are still functional but disconnected close to the blood-brain barrier, drugs that target these cells, such as lorcaserin, which targets serotonin 2C receptors on POMC cells, could still be effective.[226,227] Currently, lorcaserin is approved by the FDA for the indication of obesity. However, the EMA has withdrawn lorcaserin due to a potential risk for developing tumors (based on the results of laboratory tests), together with the potential risk of psychiatric disorders and valvulopathy. If the mediobasal hypothalamic neurons are destroyed, drugs that target their downstream pathways may be an appropriate choice. Melanocortin receptor agonists or NPY receptor antagonists should be considered when they become available for clinical treatment because POMC and AgRP/NPY neurons comprise the major neural populations in the mediobasal hypothalamus that are implicated in regulation of feeding behavior.[228,229] Setmelanotide is a novel MC4R agonist with therapeutic efficacy in POMC-deficient obese and in heterozygote *MC4R* loss-of-function carriers with obesity.[230] Setmelanotide can be a novel candidate drug to treat patients with HO.

Intranasal oxytocin is currently being explored as an anorexic agent. In a clinical study using healthy volunteers, intranasal oxytocin administration suppressed the appearance of hypothalamic activation on functional MRI scans when shown high-caloric food vs low-caloric food cues.[231] This finding was clinically replicated in healthy male patients, as caloric intake, especially that of highly palatable foods, was decreased after a single dose of oxytocin.[232,233] However, beneficial effects on weight were not observed in patients with Prader-Willi syndrome.[234,235] A recent report of oxytocin administration (combined with the opioid antagonist naltrexone) in a 13-year-old patient with CP (publication date after date of systematic literature search) reported a beneficial effect on hyperphagia and reduced BMI after 38 weeks of intervention.[187] Larger placebo-controlled cohort studies are needed to validate beneficial effects of oxytocin. Because oxytocin is a peptide, it is anticipated that intranasal administration more efficiently enters the cerebrospinal fluid (CSF) than do intravenous injections, as intravenous oxytocin must pass through the blood-brain barrier. However, physiologic evidence for this administration route is currently lacking, and similar CSF levels of oxytocin were reported in nonhuman primates after intranasal or intravenous administration of oxytocin.[236]

C. Sleep disturbances

Assessment of sleep disturbances

Sleep disturbances in patients with CP may be caused by "primary" hypothalamic dysfunction (i.e. hypersomnia, narcolepsy, disturbed sleep-wake cycles) or may be "secondary" to HO, such as obstructive sleep apnea (OSA). Patterns of sleep disturbances should be evaluated with parents or partners. If sleep disturbances are suspected, the use of a sleep log or diary is

indicated to assess sleeping patterns for at least 1 week.[237] Additionally, an actigraphy device, a wristwatch-like device, can be used to monitor movements during the day and at night in the home environment. A validated questionnaire that assesses daytime somnolence specifically is the Epworth sleepiness score.[238,239] More thorough measurement of daytime sleepiness, either narcolepsy or hypersomnia, can be obtained by the multiple sleep latency test.[240] In patients with CP, secondary narcolepsy may resemble some idiopathic forms, including increased sleep-onset rapid eye movement periods (SOREMPs) and low CSF orexin levels.[241-243] Polysomnography monitors sleep cycles and can identify if and when the sleep pattern is disrupted. Sleep-related breathing disorders, such as the presence of OSA or disruption of the sleep-wake cycle, can also be detected by polysomnography.[244] Although circadian phase markers, such as melatonin and cortisol, are associated with sleeping patterns in patients with CP, they are currently not routinely used for diagnosing disturbances in sleep-wake cycles in the general population.[103,104,245]

Interventions targeting sleep disturbances

The first step to target sleep disturbances in patients with CP are similar to those of the general population and include behavioral and psychologic interventions (recommendation, existing guidelines).[245-248] Increasing melatonin concentrations is a potential target for sleep interventions to improve sleep during the night. Altered melatonin secretion has been reported in patients with CP, which may result in earlier and more frequent waking during the night. The use of melatonin was reported in one study that included 10 patients.[104] This resulted in improved daytime sleepiness and physical activity, but outcome parameters on sleep or weight were not reported, and it is unknown how long the patients received melatonin therapy. According to existing guidelines, the sleep-promotor melatonin may be considered for children and adults with HO and circadian rhythm sleep wake disorders, to improve daytime somnolence (recommendation, existing guidelines).[249]

Daytime somnolence is another potential target for sleep interventions. Two studies in the systematic review reported sleep disturbances together with effects on weight. The use of dextroamphetamine in the first study improved daytime somnolence in all patients.[146] In a second case report, neither of the serotonergic agents tested, fluoxetine and fenfluramine, improved disturbed sleep-wake cycles or daytime somnolence. Following existing guidelines, combinations of long- and short-acting forms of stimulants may be indicated and effective for daytime somnolence and narcolepsy in adults.[250] Such stimulants include amphetamines (increase dopamine and noradrenaline release), methylphenidate (blocks dopamine reuptake), and modafinil (promotes nonamphetamine wakefulness, probably involved in dopamine reuptake inhibition). Several other studies reported effects on sleep after sleep interventions in patients with CP and other suprasellar tumors but did not include BMI change as an outcome and therefore were not selected for systematic review. In one case series, four of five patients with

CP and somnolence experienced improved daytime sleepiness after modafinil treatment.[251] In another study, seven pediatric patients with central nervous tumors (including suprasellar tumors) who received stimulants experienced improved sleepiness.[252] In a third case series, modafinil, either alone or combined with dextroamphetamine, drastically improved daytime somnolence in three children with a history of suprasellar tumors and severe narcolepsy.[243] The largest and most recent study reported significant improvements in daytime wakefulness after stimulant use in 37 brain tumor survivors (n = 16 with CP).[113] According to existing guidelines and evidence from clinical studies, the stimulants dextroamphetamine, methylphenidate and modafinil may be considered for children and adults with HO and daytime somnolence (recommendation, existing guideline, supported by clinical studies[250]). This is the only recommendation that is partially based on clinical studies that we did not directly derive from the systematic review and have not reported beneficial effects on weight. However, we think that the evidence in patients with CP is in agreement with existing guidelines of the general population and of high enough quality to recommend treatment options to improve daytime somnolence, regardless of their effects on weight.

A third target for sleep intervention is OSA, and guidelines for diagnosis and management options are available for both the pediatric and adult population (recommendation, existing guidelines).[244,253] The prevalence of OSA in patients with CP who are obese is ~46%, although it is unknown whether this is higher than in the general population, as the prevalence of OSA in BMI-matched controls ranged between 0% and 61% in two studies.[251,254] However, different criteria may be necessary for patients with CP. In a BMI matched-control study, adolescent patients with CP had significantly higher apnea-hypopnea index (AHI) scores.[254] They also experienced more frequent obstructive episodes and lower oxygen saturation during both rapid eye movement and non-rapid eye movement sleep than did BMI-matched controls. The higher AHI in patients with CP was not confirmed in another matched-controlled study.[251] However, in this study, BMI and AHI were not associated, suggesting that obesity is not the only driver of OSA in patients with CP. The benefits of continuous positive airway pressure therapy were reported for 12 patients who are obese with CP and OSA.[251] In 8 of 12 patients compliant to continuous positive airway pressure therapy, improvements in daytime sleepiness were reported. Two patients also experienced significant weight loss.

Recommendations to target sleep disturbances

- Initial behavioral and psychologic interventions should be considered to improve sleep quality and quantity and to improve daytime somnolence in children and adults with CP or other suprasellar tumors with HO and sleep disturbances (existing guidelines[245-248]).

- Melatonin may be considered in children and adults with CP or other suprasellar tumors with HO and circadian rhythm sleep wake disorders to improve daytime somnolence (existing guideline[249]).
- Stimulants, including dextroamphetamine, modafinil, and methylphenidate, may be considered to improve daytime sleepiness in children and adults with CP or other suprasellar tumors with HO (existing guideline, supported by clinical studies[250]).
- OSA assessments should be performed with a low threshold, and treatment options should be considered for children and adults with CP or other suprasellar tumors with HO (existing guidelines[244,253]).

Future interventions for sleep disturbances

Both assessment and treatment of sleep disturbances are currently unexplored for patients with CP and suprasellar tumors. Melatonin secretion may be associated with BMI and daytime somnolence in patients with CP.[255] However, findings describing melatonin deficiency are contradictory.[103,104,256,257] It is also possible that different melatonin secretion patterns occur in patients with CP and other suprasellar tumors. Absence of a melatonin peak or irregularities in phase-shifted peak melatonin levels have been observed in patients with suprasellar tumors.[103,256,258] Future large cohort studies should focus on 24-hour melatonin secretion patterns and other circadian phase markers to better predict whether and which patients may benefit from melatonin supplementation.

Secondary narcolepsy, a more acute form of daytime somnolence, also occurs in patients with CP. The clinical characteristics of secondary narcolepsy in patients with suprasellar tumors is diverse: cataplexy, decreased orexin CSF concentrations, and SOREMPs can be present, but have only been reported in small case series.[243,259-261] In a case series by Müller *et al.*, 3 of 10 patients with CP experienced hypersomnia, and 4 had repeated episodes of SOREMPs, indicative of secondary narcolepsy.[242] The heterogeneous presentation and required testing modalities may currently lead to underdiagnoses of secondary narcolepsy in this population. As secondary narcolepsy may be an amenable target for treatment, future larger studies may provide a clearer overview of the prevalence and characteristics of narcolepsy in patients with CP and other suprasellar tumors.

A group of new agents targeting sleep disorders in the general population that may be promising for patients with CP and other suprasellar tumors include melatonin receptor agonists, such as ramelteon, circadin (a prolonged-release melatonin agonist), agomelatine, and tasimelteon (used for circadian rhythm sleeping disorders).[262] A promising agent for OSA includes dronabinol, a nonselective agonist of cannabinoid type I and II receptors.[263] Whether these drugs beneficially target sleep disturbances and can be safely used specifically in patients with CP or other suprasellar tumors should be studied in the future.

D. Energy expenditure

Assessment of decreased energy expenditure

Numerous self-report questionnaires are available to measure physical activity, although their reliability and validity are generally low.[264] More objective measurements can be obtained in the home environment by monitoring heart rate or using motion sensors, which detect motion or acceleration of a limb or trunk. In clinical settings, indirect calorimetry can assess energy expenditure by measuring CO_2 production and O_2 consumption. The gold standard for measuring total energy expenditure is the double-labeled water method, which measures urine output of the orally consumed isotopes ^{2}H and ^{18}O.[265]

Interventions targeting energy expenditure

Individualized daily exercise schemes should be developed for patients with CP or other suprasellar tumors by an experienced physiotherapist. Physical activity is integrated with dietary and psychosocial support in a combined lifestyle intervention that is recommended as the cornerstone for obesity treatment of both children and adults (recommendation, existing guidelines).[196,197] Pharmacotherapeutic agents that increase energy expenditure are the most promising agents for increasing metabolic rate. Sympathomimetic agents, such as dextroamphetamines, methylphenidate, and caffeine/epinephrine stimulate the sympathetic nervous system by increasing heart rate and blood pressure. In contrast, mazindol is also a stimulant, but its effects on the cardiovascular system are more limited. Thyroid hormones are also key regulators of metabolic rate and act both peripherally and centrally.

Four studies in the systematic review evaluated markers of metabolic activity after stimulant use. Increased physical activity was reported after dextroamphetamine treatment in two studies (weak recommendation, clinical evidence).[138,146] School performance and/or energy levels improved after supraphysiologic T3 administration in one study, although BAT activity did not increase in another study after supraphysiologic T3 administration.[138,146,157,167] In general, a hyperthyroid state may cause osteoporosis, cardiovascular symptoms (*i.e.*, tachycardia, atrial fibrillation, and cardiovascular collapse), and neuropsychiatric symptoms.[266] In one study, T3 supplementation resulted in very high total T3 levels in all three patients (converted in SI units; 4.3 nmol/L, 7.5 nmol/L and 6.1 nmol/L; normal range, 0.9 to 2.8 nmol/L).[167] No signs of hyperthyroidism or thyrotoxicosis were reported, and BMD (assessed in one patient) even improved. In a case report by van Santen *et al.*, mean plasma T3 concentrations were elevated (3.2 nmol/L; normal range, 1.3 to 2.6 nmol/L), but no differences in heart rate or physical well-being were noted.[157] In both studies, no adverse effects of hyperthyroidism were reported during the intervention period, but follow-up data after the end of T3 supplementation were not reported. Therefore, any possible long-term adverse effects from T3 supplementation remain unclear.

Recommendations to target energy expenditure

- A combined lifestyle intervention, including daily physical exercise, should be included in all management approaches for HO in children and adults with CP or other suprasellar tumors (existing guidelines[196,197]).
- Dextroamphetamine may be considered for children and adults with CP or other suprasellar tumors with HO and decreased energy expenditure (weak recommendation).

Future interventions for energy expenditure

Activation of peripherally located BAT is a potential target for obesity treatment, especially in patients with extensive CP-associated hypothalamus damage. BAT activity is measured with positron emission tomography-computed tomography using radiotracers (^{18}F-fluorodeoxyglucose). BAT activity is associated with BMI, and obese men have reduced cold-induced BAT activity than do men with healthy weights.[267] Although cold temperatures may increase BAT activity, other more achievable clinical targets in patients with CP include the β-adrenergic system.[268] β3 adrenoceptors are located on the brown adipocyte cell surface and are activated by norephinephrine.[269] The β3 agonist mirabegron was recently demonstrated to activate BAT and increase the resting metabolic rate in humans.[270] β3 adrenoceptors are also expressed in white adipose tissue, myocardium, smooth muscle tissue, and liver. Therefore, the potential side effects from off-target effects in other tissues should be explored in future studies.

Altering norepinephrine levels may also effectively induce BAT activity. Atomoxetine is a selective blocker of the presynaptic norepinephrine transporter that has been shown to induce modest weight loss in obese women, patients with binge-eating disorder, and an obese boy with an *MC4R* mutation.[271-273] Activation of peroxisome proliferator-activated receptor *γ*(PPAR-*γ*) is also a promising target for BAT activation, as PPAR-γ is a key regulator of differentiation with the potential of white-to-brown fat conversion. Rosiglitazone is a PPAR-γ ligand currently used for T2DM management that induces mRNA expression of several brown fat-specific genes *in vitro*.[274] Increasing amounts of BAT is another possibility for improving energy expenditure in patients with CP. This may be achieved by BAT transplantation, although this is still in a very experimental phase.[275]

E. Hyperinsulinemia

Assessment of hyperinsulinemia

Hyperinsulinemia may occur in patients with CP due to increased vagal tone. Increased insulin concentrations may result in increased storage of fat. Obesity itself increases the risk of insulin resistance and development of T2DM. Therefore, excessive insulin secretion may induce obesity or it may be the result of obesity itself. Distinguishing between the causes and consequences of obesity is challenging, and overlap most likely exists.

Risk factors and clinical signs of hyperinsulinemia/insulin resistance, such as acanthosis nigricans, should be assessed. The gold standard for measuring hyperinsulinemia is the hyperinsulinemic euglycemic clamp, which measures whole-body insulin sensitivity *in vivo*. However, this methodology is very time-consuming and expensive. Surrogate markers for hyperinsulinemia are fasting or stimulated glucose and insulin concentrations. Indices for hyperinsulinemia/insulin resistance can be calculated via the HOMA-IR or quantitative insulin sensitivity check index, but are especially suitable for research purposes.[276]

Interventions targeting hyperinsulinemia

Lifestyle interventions with caloric restriction and physical exercise are the first interventions that should be recommended for patients with CP-associated HO, as is recommended for treatment of obesity in the general population (recommendation, existing guidelines).[277-281] Several agents that influence insulin secretion from the pancreas (directly or indirectly) or muscle, fat, and liver sensitivity to insulin are available. Agents that directly inhibit insulin release most effectively target vagus nerve–mediated hyperinsulinemia in patients with CP. Diazoxide inhibits insulin release through its action on potassium channels, and octreotide limits insulin release by binding to somatostatin receptors on the β-cell membrane.[282] Indeed, both octreotide and diazoxide had the ability to decrease insulin concentrations in patients with CP. However, this was accompanied by increased basal and/or stimulated glucose levels in most studies, with the development of diabetes mellitus in three patients after diazoxide monotherapy. Consequently, we discourage this agent for HO management in patients with CP or other suprasellar tumors (weak recommendation, clinical evidence). No weight loss occurred after octreotide in the placebo-controlled study and after diazoxide monotherapy, but one study reported reduced weight and prevalence of impaired glucose tolerance after combined diazoxide and metformin treatment. Directly targeting insulin release may not be suitable for HO treatment in patients with CP or other suprasellar tumors, and it may be questioned if vagus nerve-mediated hyperinsulinemia is a major contributing factor in the pathogenesis of HO. Importantly, note that octreotide and diazoxide are currently not FDA or EU approved for obesity.

GLP-1 agonists may be more suitable for patients with CP because they affect insulin secretion indirectly via their glucose-dependent mechanism of action. Indeed, improved HbA1c levels and weight loss occurred after GLP-1 administration (weak recommendation, clinical evidence). However, weight loss was not observed in one prospective open-label study including patients with HbA1c levels <7%.[136] Therefore, patients with CP and disturbed glucose metabolism are most likely to benefit from GLP-1 agonists. However, the GLP-1 agonist liraglutide reduced weight in a large population of obese individuals without T2DM.[283] Liraglutide is currently the only FDA- and EMA-approved GLP-1 agonist for obesity in adults, although higher doses are prescribed compared with T2DM management to induce the dose-dependent weight loss.

Other agents that primarily improve insulin sensitivity may also be considered for patients with CP. Metformin is a biguanide antihyperglycemic agent that decreases hepatic glucose production and glucose absorption and improves insulin sensitivity by increasing insulin-mediated glucose uptake.[284] Metformin may also reduce food intake by decreasing NPY- and AgRP-expressing neurons in the hypothalamus or by stimulating GLP-1 secretion.[285] Fenofibrate is a PPAR-α agonist, and pioglitazone is a PPAR-γ agonist. PPAR-α regulates lipid and carbohydrate metabolism, whereas PPAR-γ improves insulin sensitivity and glucose homeostasis.[286] Two studies of patients with CP who were treated with either metformin with fenofibrate or pioglitazone reported decreased HOMA-IR without beneficial effects on weight.[140,165] Importantly, note that most of these antidiabetic agents, including GLP-1 agonists, as well as octreotide and diazoxide, have been studied only for relatively short periods. The short-term follow-up periods of many studies result in significant knowledge gaps about the long-term benefits and adverse effects of many of these agents.

Recommendations to target hyperinsulinemia (including insulin resistance)

- A combined lifestyle intervention and weight loss are recommended to decrease hyperinsulinemia secondary to obesity in children and adults (existing guidelines[277-279,281]).
- The use of diazoxide is discouraged for children and adults with CP or other suprasellar tumors with HO and hyperinsulinemia because of increased risk for hyperglycemia and diabetes mellitus (weak recommendation).
- GLP-1 agonists may be considered for adults with CP or other suprasellar tumors with HO and hyperinsulinemia. In case they have not been FDA or EMA approved for the indication obesity, they should only be considered in the context of an ethically approved research study (weak recommendation).

Future interventions for hyperinsulinemia and insulin resistance

GLP-1 agonists appear to be generally very promising agents to target both T2DM and obesity. Several clinical trials are currently underway that will most likely extend indications for several GLP-1 agonists and optimize doses for weight management. A new GLP-1 agonist semaglutide, structurally similar to liraglutide but with a longer half-life, has demonstrated beneficial effects on weight loss.[287] The preliminary results of a recent RCT including participants with obesity, but without T2DM reported dose-dependent weight loss after 1 year[288] that was larger than that of a control group using liraglutide. Although these results appear very promising, they should be validated in future studies. Studies reporting the use of GLP-1 agonists in children are very limited, and none of the studies included in our systematic review included pediatric patients with CP. Currently, metformin and insulin are the only antidiabetic agents approved for clinical use in children. Clinical trials are currently recruiting obese pediatric patients, including those

with CP and Prader-Willi syndrome, to assess the efficacy of exenatide and liraglutide for weight management.

F. Hypopituitarism

Assessment of hypopituitarism

Timely detection and treatment of hypopituitarism can prevent exacerbation of impaired metabolic activity. Diagnosing hypopituitarism in patients with CP must be performed according to existing guidelines.[289,290] However, several pitfalls exist in the detection of hypopituitarism in patients with CP or other suprasellar tumors. In children, GH deficiency may be overlooked because of the "growth without growth hormone" phenomenon. Adequate growth may be apparent in pediatric patients with CP, despite having GH deficiency, which may be explained by elevated leptin and/or insulin levels that can induce linear growth.[291] Additionally, increased fat tissue may lead to increased synthesis of estrogens that increase growth velocity. GH deficiency is also often underdiagnosed in cases of precocious puberty. The height velocity induced by puberty may be mistakenly interpreted as adequate according to growth charts if pubertal staging is not performed, and if untreated, it may severely affect final height.[292]

Interventions targeting hypopituitarism

Patients with hypopituitarism must be treated with exogenous administration of the deficient hormones according to existing guidelines and recommendations (recommendation, existing guidelines).[289,290] To influence metabolic state, several additional interventions may be considered. We used stringent criteria (*i.e.*, study populations >100 patients with CP) for the selection of studies that reported GH interventions. This may have potentially introduced bias. However, large cohort studies permit more robust statistical analyses and improve the quality of evidence. Of the two studies we identified, one included a cohort of pediatric patients with CP and reported significantly increased height and weight with stable BMIs after 3 years of GH treatment.[147] However, the BMIs of the cohort at baseline were relatively low, and no subanalyses were performed for patients who are obese. Additionally, no other parameters of body composition were reported. Therefore, the true potential of GH treatment of patients with CP who are obese is unclear. Administration of GH appears to be safe for children with a history of CP or other suprasellar tumors, without increasing the risk of recurrence, and it is recommended in case of GH deficiency (weak recommendation, clinical evidence).[293-295]

A second study included adult patients with CP. After 5 years of GH therapy, BMIs were increased in both male and female patients. However, other parameters of body composition, such as waist circumference and fat mass, remained stable in both sexes after 5 years of intervention. Lean body mass increased only in female patients but remained stable in male patients after 5 years of GH therapy. As only descriptive analyses were used in this study, no adjustments were applied

for potential confounders, such as the contribution of untreated or inappropriately treated hypopituitarism or differences in body composition among subjects. It is therefore unknown whether a subgroup of adult patients with CP would benefit from GH treatment in terms of weight loss. As other markers of body composition remained stable during treatment, GH may be considered in adults to improve their metabolic profiles.

We did not find any studies examining the effects of levothyroxine administration to improve BMI. It is recommended that free T4 concentrations should be maintained in the middle to upper half of the reference range in patients with central hypothyroidism, although it is unknown how this beneficially affects BMI (recommendation, existing guideline).[289] Hydrocortisone overreplacement may negatively affect BMI. Upregulation of 11β-hydroxysteroid dehydrogenase type 1 activity, which increases cortisone to cortisol conversion, is present in patients with CP.[127] This may imply that lower levels of glucocorticoid replacement therapy may be sufficient for patients with CP, which may also beneficially affect BMI (recommendation, expert opinion). However, this must be balanced with the risk of hypoglycemia, adrenal crisis, and lack of energy. The guidelines for hormonal replacement in adult hypopituitarism recommend testosterone replacement to reduce fat mass and improve muscle mass in males.[289] Additionally, testosterone therapy induces puberty in boys who have not undergone (complete) pubertal development, but also improves sexual functioning, well-being, and BMD in hypogonadal males. Recommendations indicate to aim for testosterone concentrations in the mid-normal range, as overreplacement may increase the risk of prostate cancer and cardiovascular disease.[296] In girls, timely induction of puberty is important to achieve a higher peak bone mass. Additionally, treatment with estrogen reduces cardiovascular risk and mortality in premenopausal women.[289] Individualized therapeutic schedules for administering desmopressin in patients with diabetes insipidus is recommended.[289] Excess fluid intake may promote weight gain when sugar-sweetened beverages are consumed.

Recommendations to target hypopituitarism

- Adequate exogenous administration of the deficient hormones is necessary to treat hypopituitarism in children and adults with CP or other suprasellar tumors with HO (existing guidelines [289,290]).
- GH therapy may be considered for children with CP or other suprasellar tumors with HO and GH deficiency (weak recommendation).
- Levothyroxine doses sufficient to achieve free T4 levels in the middle to upper half of the reference range may be considered for children and adults with CP or other suprasellar tumors with HO and central hypothyroidism (existing guideline [289]).
- Glucocorticoid overreplacement should be avoided for children and adults with CP or other suprasellar tumors with HO and central adrenal insufficiency. Low-normal hydrocortisone doses

sufficient to prevent weight gain may be considered, while avoiding the risk for hypoglycemia and adrenal crisis (expert opinion).

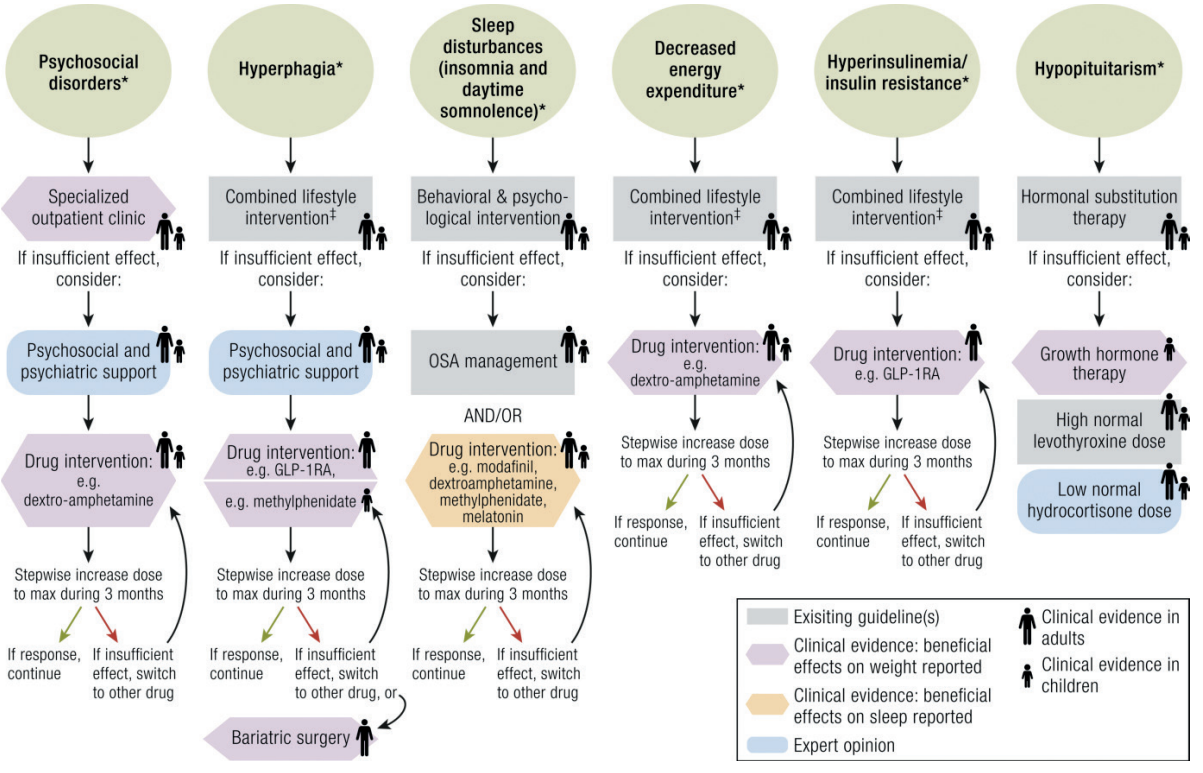
Future interventions for hypopituitarism

Early detection and timely treatment of pituitary insufficiencies are the cornerstones for targeting the consequences of hypopituitarism. Future studies should evaluate whether increasing free T4 and attenuating hydrocortisone concentrations affect BMI. Central hypothyroidism may be overlooked in patients with CP and low to moderate free T4 levels. For this reason, future studies should evaluate whether levothyroxine is beneficial in all patients with CP with low to moderate free T4 levels.[297]

Individualized treatment algorithm

We combined the findings of responders from the intervention studies from our evidence-based search with the clinical domains described above to develop an individualized treatment algorithm for patients with CP or other suprasellar tumors. After careful assessment of individual patients, interventions may be started in one or more of the six appropriate clinical domains (Figure 3). In each step of the treatment algorithm, beneficial effects on weight in either children, adults, or both are indicated. It may be prudent to apply certain intervention steps that have been studied only in a specific age group to other age categories. However, this should be done with caution, as adverse effects may differ for specific age groups (*e.g.*, bariatric surgery in children or dextroamphetamine use in adults). In agreement with existing guidelines, we recommend an initial trial of drug interventions for 3 months with a stepwise increase in dose up to the maximum tolerated dose.[196,197] If no beneficial effects on weight are apparent after 3 months, switching to another antiobesity agent is recommended. Beneficial effects on weight should be determined by health care providers and may differ among individual patients. For example, weight stabilization may be considered a considerably positive response for a patient with rapidly progressive weight gain. Although this treatment algorithm uses an in-depth approach to provide obesity management strategies for the challenging problem of HO in patients with CP or other suprasellar tumors, the choice for each intervention should be decided together with the health care provider and the patient. Interventions included in the algorithm may lack data on long-term beneficial or adverse effects and may represent only modest results in certain individuals (responders) or may be generated from studies with a high risk of bias. Drugs that are currently not FDA or EMA approved for the indication obesity are not recommended, unless they are the subject of testing in ethically approved clinical trials.

Figure 3. Individualized stepwise treatment algorithm



The first step is to identify clinical symptoms of the patient in the six domains (i.e., psychosocial disorders, hyperphagia, sleep disturbances, decreased energy expenditure, hyperinsulinemia/insulin resistance, and hypopituitarism). In many patients with CP or suprasellar tumors, symptoms within different clinical domains are present simultaneously. Recommended initial interventions are located below each clinical domain in the treatment algorithm. If the effect of the intervention is insufficient, the next step in the algorithm should be pursued. For drug interventions, a stepwise increase in dose up to the maximum tolerated dose is recommended for the first 3 mo. All interventions are categorized as clinical evidence (hexagons), existing guidelines (rectangles), or expert opinion (rectangles, round). *Methodologies for assessment of each clinical domain have been reported in the main body of the text. ‡Combined lifestyle intervention includes dietary, physical activity, and behavioral support. GLP1-RA, GLP-1 receptor agonist.

Conclusion

Although the overall evidence for HO interventions in patients with CP was modest, beneficial individual effects may be present. By identifying the correct clinical domains to target and using the proposed individualized treatment algorithm, improvements of HO and HO-associated comorbidities may be achieved. New targets for HO interventions were explored to improve future management of HO, but international collaborations enabling multicenter prospective intervention studies are still needed.

References

1. Müller HL, Merchant TE, Puget S, Martinez-Barbera JP. New outlook on the diagnosis, treatment and follow-up of childhood-onset craniopharyngioma. *Nature reviews. Endocrinology.* 2017.
2. Zacharia BE, Bruce SS, Goldstein H, Malone HR, Neugut AI, Bruce JN. Incidence, treatment and survival of patients with craniopharyngioma in the surveillance, epidemiology and end results program. *Neuro-oncology.* 2012;14(8):1070-1078.
3. Sterkenburg AS, Hoffmann A, Gebhardt U, Warmuth-Metz M, Daubenbuchel AM, Muller HL. Survival, hypothalamic obesity, and neuropsychological/psychosocial status after childhood-onset craniopharyngioma: newly reported long-term outcomes. *Neuro-oncology.* 2015;17(7):1029-1038.
4. Wijnen M, van den Heuvel-Eibrink MM, Janssen J, et al. Very long-term sequelae of craniopharyngioma. *European journal of endocrinology.* 2017;176(6):755-767.
5. Müller HL, Bruhnken G, Emser A, et al. Longitudinal study on quality of life in 102 survivors of childhood craniopharyngioma. *Child's nervous system.* 2005;21(11):975-980.
6. Olsson DS, Andersson E, Bryngelsson IL, Nilsson AG, Johannsson G. Excess mortality and morbidity in patients with craniopharyngioma, especially in patients with childhood onset: a population-based study in Sweden. *The Journal of clinical endocrinology and metabolism.* 2015;100(2):467-474.
7. Wijnen M, Olsson DS, van den Heuvel-Eibrink MM, et al. Excess morbidity and mortality in patients with craniopharyngioma: a hospital-based retrospective cohort study. *European journal of endocrinology.* 2018;178(1):95-104.
8. Haliloglu B, Atay Z, Guran T, et al. Risk factors for mortality caused by hypothalamic obesity in children with hypothalamic tumours. *Pediatr Obes.* 2016;11(5):383-388.
9. Muller HL, Emser A, Faldum A, et al. Longitudinal study on growth and body mass index before and after diagnosis of childhood craniopharyngioma. *J Clin Endocrinol Metab.* 2004;89(7):3298-3305.
10. Lustig RH, Post SR, Srivannaboon K, et al. Risk factors for the development of obesity in children surviving brain tumors. *J Clin Endocrinol Metab.* 2003;88(2):611-616.
11. Cohen M, Guger S, Hamilton J. Long term sequelae of pediatric craniopharyngioma - literature review and 20 years of experience. *Front Endocrinol (Lausanne).* 2011;2:81.
12. Joly-Amado A, Cansell C, Denis RG, et al. The hypothalamic arcuate nucleus and the control of peripheral substrates. *Best practice & research. Clinical endocrinology & metabolism.* 2014;28(5):725-737.
13. King BM. The rise, fall, and resurrection of the ventromedial hypothalamus in the regulation of feeding behavior and body weight. *Physiol Behav.* 2006;87(2):221-244.
14. Elowe-Gruau E, Beltrand J, Brauner R, et al. Childhood craniopharyngioma: hypothalamus-sparing surgery decreases the risk of obesity. *J Clin Endocrinol Metab.* 2013;98(6):2376-2382.
15. Beltran C, Roca M, Merchant TE. On the benefits and risks of proton therapy in pediatric craniopharyngioma. *International journal of radiation oncology, biology, physics.* 2012;82(2):e281-287.
16. Gump JM, Donson AM, Birks DK, et al. Identification of targets for rational pharmacological therapy in childhood craniopharyngioma. *Acta neuropathologica communications.* 2015;3:30.
17. Larkin S, Karavitaki N. Recent advances in molecular pathology of craniopharyngioma. *F1000Research.* 2017;6:1202.
18. Vemurafenib and cobimetinib in treating patients with braf v600e mutation positive craniopharyngioma. Available at: www.clinicaltrials.gov/ct2/show/NCT03224767?cond=craniopharyngioma&rank=9. Accessed 12 March 2017
19. Cohen LE. Update on childhood craniopharyngiomas. *Current opinion in endocrinology, diabetes, and obesity.* 2016;23(4):339-344.

20. Muller HL. Risk-adapted, long-term management in childhood-onset craniopharyngioma. *Pituitary.* 2016.
21. Haliloglu B, Bereket A. Hypothalamic obesity in children: pathophysiology to clinical management. *Journal of pediatric endocrinology & metabolism.* 2015;28(5-6):503-513.
22. Bereket A, Kiess W, Lustig RH, et al. Hypothalamic obesity in children. *Obes Rev.* 2012;13(9):780-798.
23. Shah E, Lodh R, Siddell P, Morrall MC. Interventions for managing weight change following paediatric acquired brain injury: a systematic review. *Dev Med Child Neurol.* 2016;58(10):1004-1008.
24. Wang KW, Chau R, Fleming A, et al. The effectiveness of interventions to treat hypothalamic obesity in survivors of childhood brain tumours: a systematic review. *Obesity reviews.*. 2017;18(8):899-914.
25. Adan RA, Vanderschuren LJ, la Fleur SE. Anti-obesity drugs and neural circuits of feeding. *Trends Pharmacol Sci.* 2008;29(4):208-217.
26. Rada P, Mendialdua A, Hernandez L, Hoebel BG. Extracellular glutamate increases in the lateral hypothalamus during meal initiation, and GABA peaks during satiation: microdialysis measurements every 30 s. *Behav Neurosci.* 2003;117(2):222-227.
27. Rowland NE, Miceli MO, Malsbury CW, et al. Medial hypothalamic lesions in Syrian hamsters: characterization of hyperphagia and weight gain. *Physiol Behav.* 1986;36(3):513-521.
28. Gao Q, Horvath TL. Neurobiology of feeding and energy expenditure. *Annual review of neuroscience.* 2007;30:367-398.
29. Michaud JL, Boucher F, Melnyk A, et al. Sim1 haploinsufficiency causes hyperphagia, obesity and reduction of the paraventricular nucleus of the hypothalamus. *Human molecular genetics*. 2001;10(14):1465-1473.
30. Swaab DF, Purba JS, Hofman MA. Alterations in the hypothalamic paraventricular nucleus and its oxytocin neurons (putative satiety cells) in Prader-Willi syndrome: a study of five cases. *J Clin Endocrinol Metab.* 1995;80(2):573-579.
31. Kublaoui BM, Gemelli T, Tolson KP, Wang Y, Zinn AR. Oxytocin deficiency mediates hyperphagic obesity of Sim1 haploinsufficient mice. *Mol Endocrinol.* 2008;22(7):1723-1734.
32. Diano S, Horvath B, Urbanski HF, Sotonyi P, Horvath TL. Fasting activates the nonhuman primate hypocretin (orexin) system and its postsynaptic targets. *Endocrinology.* 2003;144(9):3774-3778.
33. Herve C, Fellmann D. Changes in rat melanin-concentrating hormone and dynorphin messenger ribonucleic acids induced by food deprivation. *Neuropeptides.* 1997;31(3):237-242.
34. Burdakov D, Gerasimenko O, Verkhratsky A. Physiological changes in glucose differentially modulate the excitability of hypothalamic melanin-concentrating hormone and orexin neurons in situ. *The Journal of neuroscience.* 2005;25(9):2429-2433.
35. Sam AH, Troke RC, Tan TM, Bewick GA. The role of the gut/brain axis in modulating food intake. *Neuropharmacology.* 2012;63(1):46-56.
36. Grill HJ. Distributed neural control of energy balance: contributions from hindbrain and hypothalamus. *Obesity.* 2006;14 Suppl 5:216S-221S.
37. Seeley RJ, Grill HJ, Kaplan JM. Neurological dissociation of gastrointestinal and metabolic contributions to meal size control. *Behav Neurosci.* 1994;108(2):347-352.
38. Blevins JE, Eakin TJ, Murphy JA, Schwartz MW, Baskin DG. Oxytocin innervation of caudal brainstem nuclei activated by cholecystokinin. *Brain Res.* 2003;993(1-2):30-41.
39. Alonso-Alonso M, Woods SC, Pelchat M, et al. Food reward system: current perspectives and future research needs. *Nutr Rev.* 2015;73(5):296-307.
40. Hernandez L, Hoebel BG. Feeding and hypothalamic stimulation increase dopamine turnover in the accumbens. *Physiol Behav.* 1988;44(4-5):599-606.

41. Belgardt BF, Okamura T, Bruning JC. Hormone and glucose signalling in POMC and AgRP neurons. *The Journal of physiology.* 2009;587(Pt 22):5305-5314.

42. Bagnasco M, Tulipano G, Melis MR, Argiolas A, Cocchi D, Muller EE. Endogenous ghrelin is an orexigenic peptide acting in the arcuate nucleus in response to fasting. *Regulatory peptides.* 2003;111(1-3):161-167.

43. Aponte Y, Atasoy D, Sternson SM. AGRP neurons are sufficient to orchestrate feeding behavior rapidly and without training. *Nat Neurosci.* 2011;14(3):351-355.

44. Krashes MJ, Koda S, Ye C, et al. Rapid, reversible activation of AgRP neurons drives feeding behavior in mice. *J Clin Invest.* 2011;121(4):1424-1428.

45. Hoffmann A, Gebhardt U, Sterkenburg AS, Warmuth-Metz M, Muller HL. Diencephalic syndrome in childhood craniopharyngioma--results of German multicenter studies on 485 long-term survivors of childhood craniopharyngioma. *J Clin Endocrinol Metab.* 2014;99(11):3972-3977.

46. Speakman JR. Evolutionary perspectives on the obesity epidemic: adaptive, maladaptive, and neutral viewpoints. *Annual review of nutrition.* 2013;33:289-317.

47. Tolson KP, Gemelli T, Gautron L, Elmquist JK, Zinn AR, Kublaoui BM. Postnatal Sim1 deficiency causes hyperphagic obesity and reduced Mc4r and oxytocin expression. *J Neurosci.* 2010;30(10):3803-3812.

48. Huszar D, Lynch CA, Fairchild-Huntress V, et al. Targeted disruption of the melanocortin-4 receptor results in obesity in mice. *Cell.* 1997;88(1):131-141.

49. Vaisse C, Clement K, Durand E, Hercberg S, Guy-Grand B, Froguel P. Melanocortin-4 receptor mutations are a frequent and heterogeneous cause of morbid obesity. *The Journal of clinical investigation.* 2000;106(2):253-262.

50. Donahoo WT, Levine JA, Melanson EL. Variability in energy expenditure and its components. *Current opinion in clinical nutrition and metabolic care.* 2004;7(6):599-605.

51. Quatela A, Callister R, Patterson A, MacDonald-Wicks L. The Energy Content and Composition of Meals Consumed after an Overnight Fast and Their Effects on Diet Induced Thermogenesis: A Systematic Review, Meta-Analyses and Meta-Regressions. *Nutrients.* 2016;8(11).

52. Monroe MB, Seals DR, Shapiro LF, Bell C, Johnson D, Parker Jones P. Direct evidence for tonic sympathetic support of resting metabolic rate in healthy adult humans. *American journal of physiology, Endocrinology and metabolism.* 2001;280(5):E740-744.

53. Gavini CK, Jones WC, 2nd, Novak CM. Ventromedial hypothalamic melanocortin receptor activation: regulation of activity energy expenditure and skeletal muscle thermogenesis. *The Journal of physiology.* 2016;594(18):5285-5301.

54. Monda M, Sullo A, De Luca V, Viggiano A, Pellicano MP. Acute lesions of the ventromedial hypothalamus reduce sympathetic activation and thermogenic changes induced by PGE1. *Journal of physiology.* 1997;91(6):285-290.

55. Marsh AJ, Fontes MA, Killinger S, Pawlak DB, Polson JW, Dampney RA. Cardiovascular responses evoked by leptin acting on neurons in the ventromedial and dorsomedial hypothalamus. *Hypertension.* 2003;42(4):488-493.

56. Leshan RL, Bjornholm M, Munzberg H, Myers MG, Jr. Leptin receptor signaling and action in the central nervous system. *Obesity.* 2006;14 Suppl 5:208s-212s.

57. Shaikh MG, Grundy RG, Kirk JM. Hyperleptinaemia rather than fasting hyperinsulinaemia is associated with obesity following hypothalamic damage in children. *European journal of endocrinology.* 2008;159(6):791-797.

58. Roth C, Wilken B, Hanefeld F, Schroter W, Leonhardt U. Hyperphagia in children with craniopharyngioma is associated with hyperleptinaemia and a failure in the downregulation of appetite. *European journal of endocrinology.* 1998;138(1):89-91.

59. Rosenbaum M, Leibel RL. Adaptive thermogenesis in humans. *Int J Obes (Lond).* 2010;34 Suppl 1:S47-55.

60. Fliers E, Boelen A, van Trotsenburg AS. Central regulation of the hypothalamo-pituitary-thyroid (HPT) axis: focus on clinical aspects. *Handbook of clinical neurology.* 2014;124:127-138.
61. Iwen KA, Schroder E, Brabant G. Thyroid hormones and the metabolic syndrome. *Eur Thyroid J.* 2013;2(2):83-92.
62. Klieverik LP, Janssen SF, van Riel A, et al. Thyroid hormone modulates glucose production via a sympathetic pathway from the hypothalamic paraventricular nucleus to the liver. *Proceedings of the National Academy of Sciences of the United States of America.* 2009;106(14):5966-5971.
63. Lopez M, Varela L, Vazquez MJ, et al. Hypothalamic AMPK and fatty acid metabolism mediate thyroid regulation of energy balance. *Nature medicine.* 2010;16(9):1001-1008.
64. Contreras C, Nogueiras R, Dieguez C, Rahmouni K, Lopez M. Traveling from the hypothalamus to the adipose tissue: The thermogenic pathway. *Redox Biol.* 2017;12:854-863.
65. Tanida M, Yamamoto N, Shibamoto T, Rahmouni K. Involvement of hypothalamic AMP-activated protein kinase in leptin-induced sympathetic nerve activation. *PloS one.* 2013;8(2):e56660.
66. Beiroa D, Imbernon M, Gallego R, et al. GLP-1 agonism stimulates brown adipose tissue thermogenesis and browning through hypothalamic AMPK. *Diabetes.* 2014;63(10):3346-3358.
67. Berthoud HR, Jeanrenaud B. Acute hyperinsulinemia and its reversal by vagotomy after lesions of the ventromedial hypothalamus in anesthetized rats. *Endocrinology.* 1979;105(1):146-151.
68. Lustig RH. Autonomic dysfunction of the beta-cell and the pathogenesis of obesity. *Reviews in endocrine & metabolic disorders.* 2003;4(1):23-32.
69. Miura Y, Gilon P, Henquin JC. Muscarinic stimulation increases Na+ entry in pancreatic B-cells by a mechanism other than the emptying of intracellular Ca2+ pools. *Biochemical and biophysical research communications.* 1996;224(1):67-73.
70. Kiba T, Tanaka K, Numata K, Hoshino M, Misugi K, Inoue S. Ventromedial hypothalamic lesion-induced vagal hyperactivity stimulates rat pancreatic cell proliferation. *Gastroenterology.* 1996;110(3):885-893.
71. Inoue H, Ogawa W, Asakawa A, et al. Role of hepatic STAT3 in brain-insulin action on hepatic glucose production. *Cell Metab.* 2006;3(4):267-275.
72. McGowan MK, Andrews KM, Grossman SP. Role of intrahypothalamic insulin in circadian patterns of food intake, activity, and body temperature. *Behavioral neuroscience.* 1992;106(2):380-385.
73. Routh VH. Glucose sensing neurons in the ventromedial hypothalamus. *Sensors (Basel, Switzerland).* 2010;10(10):9002-9025.
74. Roth CL. Hypothalamic Obesity in Craniopharyngioma Patients: Disturbed Energy Homeostasis Related to Extent of Hypothalamic Damage and Its Implication for Obesity Intervention. *J Clin Med.* 2015;4(9):1774-1797.
75. Zada G, Kintz N, Pulido M, Amezcua L. Prevalence of neurobehavioral, social, and emotional dysfunction in patients treated for childhood craniopharyngioma: a systematic literature review. *PloS one.* 2013;8(11):e76562.
76. Flynn FG, Cummings JL, Tomiyasu U. Altered behavior associated with damage to the ventromedial hypothalamus: a distinctive syndrome. *Behavioural neurology.* 1988;1(1):49-58.
77. Anderson CA, Wilkening GN, Filley CM, Reardon MS, Kleinschmidt-DeMasters BK. Neurobehavioral outcome in pediatric craniopharyngioma. *Pediatric neurosurgery.* 1997;26(5):255-260.
78. Hammond JL, Hall SS. Functional analysis and treatment of aggressive behavior following resection of a craniopharyngioma. *Developmental medicine and child neurology.* 2011;53(4):369-374.
79. Albert DJ, Dyson EM, Walsh ML. Competitive behavior in male rats: aggression and success enhanced by medial hypothalamic lesions as well as by testosterone implants. *Physiology & behavior.* 1987;40(6):695-701.

80. Skorzewska A, Lal S, Waserman J, Guyda H. Abnormal food-seeking behavior after surgery for craniopharyngioma. *Neuropsychobiology.* 1989;21(1):17-20.

81. Ondruch A, Maryniak A, Kropiwnicki T, Roszkowski M, Daszkiewicz P. Cognitive and social functioning in children and adolescents after the removal of craniopharyngioma. *Child's nervous system.* 2011;27(3):391-397.

82. Riva D, Pantaleoni C, Devoti M, Saletti V, Nichelli F, Giorgi C. Late neuropsychological and behavioural outcome of children surgically treated for craniopharyngioma. *Child's nervous system.* 1998;14(4-5):179-184.

83. Hoffmann A, Ozyurt J, Lohle K, Reichel J, Thiel CM, Muller HL. First experiences with neuropsychological effects of oxytocin administration in childhood-onset craniopharyngioma. *Endocrine.* 2017;56(1):175-185.

84. Daubenbuchel AM, Hoffmann A, Eveslage M, et al. Oxytocin in survivors of childhood-onset craniopharyngioma. *Endocrine.* 2016;54(2):524-531.

85. Hua C, Shulkin BL, Indelicato DJ, et al. Postoperative cerebral glucose metabolism in pediatric patients receiving proton therapy for craniopharyngioma. *J Neurosurg Pediatr.* 2015:1-7.

86. Kiehna EN, Mulhern RK, Li C, Xiong X, Merchant TE. Changes in attentional performance of children and young adults with localized primary brain tumors after conformal radiation therapy. *J Clin Oncol.* 2006;24(33):5283-5290.

87. Merchant TE, Kiehna EN, Kun LE, et al. Phase II trial of conformal radiation therapy for pediatric patients with craniopharyngioma and correlation of surgical factors and radiation dosimetry with change in cognitive function. *Journal of neurosurgery.* 2006;104(2 Suppl):94-102.

88. Poretti A, Grotzer MA, Ribi K, Schonle E, Boltshauser E. Outcome of craniopharyngioma in children: long-term complications and quality of life. *Dev Med Child Neurol.* 2004;46(4):220-229.

89. Pedreira CC, Stargatt R, Maroulis H, et al. Health related quality of life and psychological outcome in patients treated for craniopharyngioma in childhood. *JPEM.* 2006;19(1):15-24.

90. Dekkers OM, Biermasz NR, Smit JW, et al. Quality of life in treated adult craniopharyngioma patients. *European journal of endocrinology.* 2006;154(3):483-489.

91. Roemmler-Zehrer J, Geigenberger V, Stormann S, et al. Specific behaviour, mood and personality traits may contribute to obesity in patients with craniopharyngioma. *Clinical endocrinology.* 2015;82(1):106-114.

92. Parkinson WL, Weingarten HP. Dissociative analysis of ventromedial hypothalamic obesity syndrome. *Am J Physiol.* 1990;259(4 Pt 2):R829-835.

93. Gettys TW, Harkness PJ, Watson PM. The beta 3-adrenergic receptor inhibits insulin-stimulated leptin secretion from isolated rat adipocytes. *Endocrinology.* 1996;137(9):4054-4057.

94. Giacobino JP. Role of the beta3-adrenoceptor in the control of leptin expression. *Horm Metab Res.* 1996;28(12):633-637.

95. Roth CL, Gebhardt U, Muller HL. Appetite-regulating hormone changes in patients with craniopharyngioma. *Obesity.* 2011;19(1):36-42.

96. Kanumakala S, Greaves R, Pedreira CC, et al. Fasting ghrelin levels are not elevated in children with hypothalamic obesity. *The Journal of clinical endocrinology and metabolism.* 2005;90(5):2691-2695.

97. Roemmler-Zehrer J, Geigenberger V, Stormann S, et al. Food intake regulating hormones in adult craniopharyngioma patients. *European journal of endocrinology.* 2014;170(4):627-635.

98. Harz KJ, Muller HL, Waldeck E, Pudel V, Roth C. Obesity in patients with craniopharyngioma: assessment of food intake and movement counts indicating physical activity. *J Clin Endocrinol Metab.* 2003;88(11):5227-5231.

99. Holmer H, Pozarek G, Wirfalt E, et al. Reduced energy expenditure and impaired feeding-related signals but not high energy intake reinforces hypothalamic obesity in adults with childhood onset craniopharyngioma. *J Clin Endocrinol Metab.* 2010;95(12):5395-5402.
100. Shaikh MG, Grundy RG, Kirk JM. Reductions in basal metabolic rate and physical activity contribute to hypothalamic obesity. *The Journal of clinical endocrinology and metabolism.* 2008;93(7):2588-2593.
101. Hoffmann A, Postma FP, Sterkenburg AS, Gebhardt U, Muller HL. Eating behavior, weight problems and eating disorders in 101 long-term survivors of childhood-onset craniopharyngioma. *JPEM.* 2015;28(1-2):35-43.
102. Cajochen C, Krauchi K, Wirz-Justice A. Role of melatonin in the regulation of human circadian rhythms and sleep. *Journal of neuroendocrinology.* 2003;15(4):432-437.
103. Pickering L, Jennum P, Gammeltoft S, Poulsgaard L, Feldt-Rasmussen U, Klose M. Sleep-wake and melatonin pattern in craniopharyngioma patients. *European journal of endocrinology.* 2014;170(6):873-884.
104. Muller HL, Handwerker G, Gebhardt U, et al. Melatonin treatment in obese patients with childhood craniopharyngioma and increased daytime sleepiness. *Cancer causes & control: CCC.* 2006;17(4):583-589.
105. Gallopin T, Fort P, Eggermann E, et al. Identification of sleep-promoting neurons in vitro. *Nature.* 2000;404(6781):992-995.
106. Donlea JM, Alam MN, Szymusiak R. Neuronal substrates of sleep homeostasis; lessons from flies, rats and mice. *Curr. Opin. Neurobiol.* 2017;44:228-235.
107. Ono D, Yamanaka A. Hypothalamic regulation of the sleep/wake cycle. *Neuroscience research.* 2017;118:74-81.
108. Saper CB, Fuller PM, Pedersen NP, Lu J, Scammell TE. Sleep state switching. *Neuron.* 2010;68(6):1023-1042.
109. Lu J, Greco MA, Shiromani P, Saper CB. Effect of lesions of the ventrolateral preoptic nucleus on NREM and REM sleep. *J Neurosci.* 2000;20(10):3830-3842.
110. Jurkowlaniec E, Trojniar W, Tokarski J. Daily pattern of EEG activity in rats with lateral hypothalamic lesions. *J Physiol Pharmacol.* 1994;45(3):399-411.
111. Nishino S, Ripley B, Overeem S, Lammers GJ, Mignot E. Hypocretin (orexin) deficiency in human narcolepsy. *Lancet (London, England).* 2000;355(9197):39-40.
112. Muller HL. Increased daytime sleepiness in patients with childhood craniopharyngioma and hypothalamic tumor involvement: review of the literature and perspectives. *International journal of endocrinology.* 2010;2010:519607.
113. Khan RB, Merchant TE, Sadighi ZS, et al. Prevalence, risk factors, and response to treatment for hypersomnia of central origin in survivors of childhood brain tumors. *Journal of neuro-oncology.* 2018;136(2):379-384.
114. Greer SM, Goldstein AN, Walker MP. The impact of sleep deprivation on food desire in the human brain. *Nat Commun.* 2013;4:2259.
115. Bomer I, Saure C, Caminiti C, et al. Comparison of energy expenditure, body composition, metabolic disorders, and energy intake between obese children with a history of craniopharyngioma and children with multifactorial obesity. *JPEM.* 2015;28(11-12):1305-1312.
116. Roth CL, Hunneman DH, Gebhardt U, Stoffel-Wagner B, Reinehr T, Muller HL. Reduced sympathetic metabolites in urine of obese patients with craniopharyngioma. *Pediatric research.* 2007;61(4):496-501.
117. Ruffin M, Nicolaidis S. Electrical stimulation of the ventromedial hypothalamus enhances both fat utilization and metabolic rate that precede and parallel the inhibition of feeding behavior. *Brain research.* 1999;846(1):23-29.

118. Vella KR, Ramadoss P, Lam FS, et al. NPY and MC4R signaling regulate thyroid hormone levels during fasting through both central and peripheral pathways. *Cell metabolism.* 2011;14(6):780-790.

119. Guran T, Turan S, Bereket A, et al. The role of leptin, soluble leptin receptor, resistin, and insulin secretory dynamics in the pathogenesis of hypothalamic obesity in children. *European journal of pediatrics*. 2009;168(9):1043-1048.

120. Simoneau-Roy J, O'Gorman C, Pencharz P, Adeli K, Daneman D, Hamilton J. Insulin sensitivity and secretion in children and adolescents with hypothalamic obesity following treatment for craniopharyngioma. *Clin Endocrinol (Oxf).* 2010;72(3):364-370.

121. Pinto G, Bussieres L, Recasens C, Souberbielle JC, Zerah M, Brauner R. Hormonal factors influencing weight and growth pattern in craniopharyngioma. *Hormone research*. 2000;53(4):163-169.

122. Trivin C, Busiah K, Mahlaoui N, et al. Childhood craniopharyngioma: greater hypothalamic involvement before surgery is associated with higher homeostasis model insulin resistance index. *BMC pediatrics*. 2009;9:24.

123. Moller N, Jorgensen JO, Moller J, et al. Metabolic effects of growth hormone in humans. *Metabolism: clinical and experimental.* 1995;44(10 Suppl 4):33-36.

124. Whitlock KE. Origin and development of GnRH neurons. *Trends in endocrinology and metabolism*. 2005;16(4):145-151.

125. Holmer H, Popovic V, Ekman B, Follin C, Siversson AB, Erfurth EM. Hypothalamic involvement and insufficient sex steroid supplementation are associated with low bone mineral density in women with childhood onset craniopharyngioma. *European journal of endocrinology.* 2011;165(1):25-31.

126. Muller HL, Heinrich M, Bueb K, et al. Perioperative dexamethasone treatment in childhood craniopharyngioma--influence on short-term and long-term weight gain. *Exp Clin Endocrinol Diabetes.* 2003;111(6):330-334.

127. Tiosano D, Eisentein I, Militianu D, Chrousos GP, Hochberg Z. 11 beta-Hydroxysteroid dehydrogenase activity in hypothalamic obesity. *The Journal of clinical endocrinology and metabolism*. 2003;88(1):379-384.

128. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6(7):e1000097.

129. Higgins JPT, Green S. eds. Chapter 7: Selecting studies and collecting data. In: Higgins JP, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0. The Cochrane Collaboration; 2011. Available at: http://handbook.cochrane.org.

130. Higgins JPT, Altman DG, Sterne JA, eds. Chapter 8: Assessing risk of bias in included studies. In: Higgins JP, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0. The Cochrane Collaboration; 2011. Available at: www.handbook.cochrane.org.

131. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ.* 2016;355:i4919.

132. Schünemann H, Brozek J, Guyatt G, Oxman A, eds. GRADE handbook for grading quality of evidence and strength of recommendations. Updated October 2013. The GRADE Working Group; 2013. Available at: https://gdt.gradepro.org/app/handbook/handbook.html. Accessed 17 january 2018.

133. GRADEpro GDT: GRADEpro guideline Development Tool [Software]. McMaster University; 2015 (developed by Evidence Prime, Inc.) Available from https://gradepro.org/. Accessed 17 january 2018.

134. Guyatt GH, Oxman AD, Vist GE, et al. GRADE Working group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ.* 2008;336(7650):924-926.

135. Lustig RH, Hinds PS, Ringwald-Smith K, et al. Octreotide therapy of pediatric hypothalamic obesity: a double-blind, placebo-controlled trial. *J Clin Endocrinol Metab.* 2003;88(6):2586-2592.

136. Shoemaker A, Proietto J, Abuzzahab MJ, Markovic T, Malloy J, Kim DD. A randomized, placebo-controlled trial of beloranib for the treatment of hypothalamic injury-associated obesity. *Diabetes, obesity & metabolism*. 2017;19(8):1165-1170.

137. Brauner R, Serreau R, Souberbielle JC, et al. Diazoxide in Children With Obesity After Hypothalamic-Pituitary Lesions: A Randomized, Placebo-Controlled Trial. *J Clin Endocrinol Metab*. 2016;101(12):4825-4833.

138. Mason PW, Krawiecki N, Meacham LR. The use of dextroamphetamine to treat obesity and hyperphagia in children treated for craniopharyngioma. *Arch Pediatr Adolesc Med*. 2002;156(9):887-892.

139. Hamilton JK, Conwell LS, Syme C, Ahmet A, Jeffery A, Daneman D. Hypothalamic Obesity following Craniopharyngioma Surgery: Results of a Pilot Trial of Combined Diazoxide and Metformin Therapy. *Int J Pediatr Endocrinol*. 2011;2011:417949.

140. Kalina MA, Wilczek M, Kalina-Faska B, Skala-Zamorowska E, Mandera M, Malecka Tendera E. Carbohydrate-lipid profile and use of metformin with micronized fenofibrate in reducing metabolic consequences of craniopharyngioma treatment in children: single institution experience. *J Pediatr Endocrinol Metab*. 2015;28(1-2):45-51.

141. Lustig RH, Rose SR, Burghen GA, et al. Hypothalamic obesity caused by cranial insult in children: altered glucose and insulin dynamics and reversal by a somatostatin agonist. *J Pediatr*. 1999;135(2 Pt 1):162-168.

142. Lomenick JP, Buchowski MS, Shoemaker AH. A 52-week pilot study of the effects of exenatide on body weight in patients with hypothalamic obesity. *Obesity*. 2016;24(6):1222-1225.

143. Rakhshani N, Jeffery AS, Schulte F, Barrera M, Atenafu EG, Hamilton JK. Evaluation of a comprehensive care clinic model for children with brain tumor and risk for hypothalamic obesity. *Obesity*. 2010;18(9):1768-1774.

144. Steele CA, Cuthbertson DJ, MacFarlane IA, et al. Hypothalamic obesity: prevalence, associations and longitudinal trends in weight in a specialist adult neuroendocrine clinic. *Eur J Endocrinol*. 2013;168(4):501-507.

145. Sterkenburg AS, Hoffmann A, Gebhardt U, Waldeck E, Springer S, Muller HL. [Childhood craniopharyngioma with hypothalamic obesity - no long-term weight reduction due to rehabilitation programs]. *Klin Padiatr*. 2014;226(6-7):344-350.

146. Ismail D, O'Connell MA, Zacharin MR. Dexamphetamine use for management of obesity and hypersomnolence following hypothalamic injury. *J Pediatr Endocrinol Metab*. 2006;19(2):129-134.

147. Geffner M, Lundberg M, Koltowska-Haggstrom M, et al. Changes in height, weight, and body mass index in children with craniopharyngioma after three years of growth hormone therapy: analysis of KIGS (Pfizer International Growth Database). *J Clin Endocrinol Metab*. 2004;89(11):5435-5440.

148. Zoicas F, Droste M, Mayr B, Buchfelder M, Schofl C. GLP-1 analogues as a new treatment option for hypothalamic obesity in adults: report of nine cases. *Eur J Endocrinol*. 2013;168(5):699-706.

149. Weismann D, Pelka T, Bender G, et al. Bariatric surgery for morbid obesity in craniopharyngioma. *Clin Endocrinol (Oxf)*. 2013;78(3):385-390.

150. Wijnen M, Olsson DS, van den Heuvel-Eibrink MM, et al. Efficacy and safety of bariatric surgery for craniopharyngioma-related hypothalamic obesity: a matched case-control study with 2 years of follow-up. *Int J Obes (Lond)*. 2017;41(2):210-216.

151. Yuen KC, Koltowska-Haggstrom M, Cook DM, et al. Clinical characteristics and effects of GH replacement therapy in adults with childhood-onset craniopharyngioma compared with those in adults with other causes of childhood-onset hypothalamic-pituitary dysfunction. *Eur J Endocrinol*. 2013;169(4):511-519.

152. Meijneke RW, Schouten-van Meeteren AY, de Boer NY, et al. Hypothalamic obesity after treatment for craniopharyngioma: the importance of the home environment. *J Pediatr Endocrinol Metab.* 2015;28(1-2):59-63.

153. Lee YJ, Backeljauw PF, Kelly PD, Verdi PD, Redmond GP. Successful weight loss with protein-sparing modified fast in a morbidly obese boy with panhypopituitarism, diabetes insipidus, and defective thirst regulation. *Clin Pediatr (Phila).* 1992;31(4):234-236.

154. Jordaan GP, Roberts MC, Emsley RA. Serotonergic agents in the treatment of hypothalamic obesity syndrome: a case report. *Int J Eat Disord.* 1996;20(1):111-113.

155. Sadatomo T, Sakoda K, Yamanaka M, Kutsuna M, Kurisu K. Mazindol administration improved hyperphagia after surgery for craniopharyngioma--case report. *Neurol Med Chir (Tokyo).* 2001;41(4):210-212.

156. Elfers CT, Roth CL. Effects of methylphenidate on weight gain and food intake in hypothalamic obesity. *Front Endocrinol (Lausanne).* 2011;2:78.

157. van Santen HM, Schouten-Meeteren AY, Serlie M, et al. Effects of T3 treatment on brown adipose tissue and energy expenditure in a patient with craniopharyngioma and hypothalamic obesity. *J Pediatr Endocrinol Metab.* 2015;28(1-2):53-57.

158. Simmons JH, Shoemaker AH, Roth CL. Treatment with glucagon-like Peptide-1 agonist exendin-4 in a patient with hypothalamic obesity secondary to intracranial tumor. *Horm Res Paediatr.* 2012;78(1):54-58.

159. Thondam SK, Cuthbertson DJ, Aditya BS, Macfarlane IA, Wilding JP, Daousi C. A glucagon-like peptide-1 (GLP-1) receptor agonist in the treatment for hypothalamic obesity complicated by type 2 diabetes mellitus. *Clin Endocrinol (Oxf).* 2012;77(4):635-637.

160. Castro-Dufourny I, Carrasco R, Pascual JM. Hypothalamic obesity after craniopharyngioma surgery: Treatment with a long acting glucagon like peptide 1 derivated. *Endocrinol Diabetes Nutr.* 2017;64(3):182-184.

161. Inge TH, Pfluger P, Zeller M, et al. Gastric bypass surgery for treatment of hypothalamic obesity after craniopharyngioma therapy. *Nat Clin Pract Endocrinol Metab.* 2007;3(8):606-609.

162. Page-Wilson G, Wardlaw SL, Khandji AG, Korner J. Hypothalamic obesity in patients with craniopharyngioma: treatment approaches and the emerging role of gastric bypass surgery. *Pituitary.* 2012;15(1):84-92.

163. Smith DK, Sarfeh J, Howard L. Truncal vagotomy in hypothalamic obesity. *Lancet.* 1983;1(8337):1330-1331.

164. Harat M, Rudas M, Zielinski P, Birska J, Sokal P. Nucleus accumbens stimulation in pathological obesity. *Neurol Neurochir Pol.* 2016;50(3):207-210.

165. Igaki N, Tanaka M, Goto T. Markedly improved glycemic control and enhanced insulin sensitivity in a patient with type 2 diabetes complicated by a suprasellar tumor treated with pioglitazone and metformin. *Intern Med.* 2005;44(8):832-837.

166. Greenway FL, Bray GA. Treatment of hypothalamic obesity with caffeine and ephedrine. *Endocr Pract.* 2008;14(6):697-703.

167. Fernandes JK, Klein MJ, Ater JL, Kuttesch JF, Vassilopoulou-Sellin R. Triiodothyronine supplementation for hypothalamic obesity. *Metabolism.* 2002;51(11):1381-1383.

168. Rottembourg D, O'Gorman CS, Urbach S, et al. Outcome after bariatric surgery in two adolescents with hypothalamic obesity following treatment of craniopharyngioma. *J Pediatr Endocrinol Metab.* 2009;22(9):867-872.

169. Muller HL, Gebhardt U, Maroske J, Hanisch E. Long-term follow-up of morbidly obese patients with childhood craniopharyngioma after laparoscopic adjustable gastric banding (LAGB). *Klin Padiatr.* 2011;223(6):372-373.

170. Gatta B, Nunes ML, Bailacq-Auder C, Etchechoury L, Collet D, Tabarin A. Is bariatric surgery really inefficient in hypothalamic obesity? *Clin Endocrinol (Oxf).* 2013;78(4):636-638.

171. Bretault M, Laroche S, Lacorte JM, et al. Postprandial GLP-1 Secretion After Bariatric Surgery in Three Cases of Severe Obesity Related to Craniopharyngiomas. *Obes Surg.* 2016;26(5):1133-1137.

172. Wolf P, Winhofer Y, Smajis S, et al. Hormone Substitution after Gastric Bypass Surgery in Patients with Hypopituitarism Secondary to Craniopharyngioma. *Endocr Pract.* 2016;22(5):595-601.

173. Trotta M, Da Broi J, Salerno A, Testa RM, Marinari GM. Sleeve gastrectomy leads to easy management of hormone replacement therapy and good weight loss in patients treated for craniopharyngioma. *Updates Surg.* 2017;69(1):95-99.

174. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care.* 1992;30(6):473-483.

175. McKenna SP, Doward LC, Alonso J, et al. The QoL-AGHDA: an instrument for the assessment of quality of life in adults with growth hormone deficiency. *Qual Life Res.* 1999;8(4):373-383.

176. National Insitute for Health and Clinical Excellence. Improving Outcomes for People with Brain and Other CNS Tumours: Available at: https://www.nice.org.uk/guidance/csg10/resources/improving-outcomes-for-people-with-brain-and-other-central-nervous-system-tumours-update-27841361437. Accessed 15 January 2018.

177. Farisse J, Padovani R, Boyer L, Guedj E, Brue TH, Lanc¸on C. Modulation of secondary binge-eating disorders by topiramate: A post surgery and radiotherapy panhypopituitary case. *European Neuropsychopharmacology.* 2011;21:S554.

178. Burgos Marín R, Parra Velázquez C, Sánchez Vázquez V, Guijarro Granados T. Topiramate treatment for impulse control disorders. A case report of craniopharyngioma. *Psiquiatria Biologica.* 2003;10(5):179-182.

179. Jenkins LM, Drummond KJ, Andrewes DG. Emotional and personality changes following brain tumour resection. *Journal of clinical neuroscience.* 2016;29:128-132.

180. Harvey DW, Morrall M, Neilly E, Murdoch-Eaton D. Question 3. Should stimulants be administered to manage difficulties with attention, hyperactivity and impulsivity following paediatric acquired brain injury? *Archives of disease in childhood.* 2012;97(8):755-758.

181. Ebner NC, Lin T, Muradoglu M, et al. Associations between oxytocin receptor gene (OXTR) methylation, plasma oxytocin, and attachment across adulthood. *International journal of psychophysiology.* 2018.

182. Kosfeld M, Heinrichs M, Zak PJ, Fischbacher U, Fehr E. Oxytocin increases trust in humans. *Nature.* 2005;435(7042):673-676.

183. Domes G, Heinrichs M, Michel A, Berger C, Herpertz SC. Oxytocin improves "mind-reading" in humans. *Biological psychiatry.* 2007;61(6):731-733.

184. Guastella AJ, Einfeld SL, Gray KM, et al. Intranasal oxytocin improves emotion recognition for youth with autism spectrum disorders. *Biological psychiatry.* 2010;67(7):692-694.

185. Yatawara CJ, Einfeld SL, Hickie IB, Davenport TA, Guastella AJ. The effect of oxytocin nasal spray on social interaction deficits observed in young children with autism: a randomized clinical crossover trial. *Molecular psychiatry.* 2016;21(9):1225-1231.

186. Rice LJ, Einfeld SL, Hu N, Carter CS. A review of clinical trials of oxytocin in Prader-Willi syndrome. *Current opinion in psychiatry.* 2018;31(2):123-127.

187. Hsu EA, Miller JL, Perez FA, Roth CL. Oxytocin and Naltrexone successfully treat hypothalamic obesity in a boy post-craniopharyngioma resection. *The Journal of clinical endocrinology and metabolism.* 2017.

188. Johnson RK. Dietary intake--how do we measure what people are really eating? *Obesity research.* 2002;10 Suppl 1:63s-68s.

189. Lichtman SW, Pisarska K, Berman ER, et al. Discrepancy between self-reported and actual caloric intake and exercise in obese subjects. *The New England journal of medicine.* 1992;327(27):1893-1898.

190. Briefel RR, Sempos CT, McDowell MA, Chien S, Alaimo K. Dietary methods research in the third National Health and Nutrition Examination Survey: underreporting of energy intake. *The American journal of clinical nutrition.* 1997;65(4 Suppl):1203s-1209s.

191. National Institutes of Health. National Children's Study Dietary Assessment Literature Review. Available at: https://epi.grants.cancer.gov/past-initiatives/assess_wc/review/pdf/. Accessed 15 april 2018.

192. Heymsfield SB, Avena NM, Baier L, et al. Hyperphagia: current concepts and future directions proceedings of the 2nd international conference on hyperphagia. *Obesity (Silver Spring, Md.).* 2014;22 Suppl 1:S1-s17.

193. Russell H, Oliver C. The assessment of food-related problems in individuals with Prader-Willi syndrome. *The British journal of clinical psychology.* 2003;42(Pt 4):379-392.

194. Lowe MR, Butryn ML, Didie ER, et al. The Power of Food Scale. A new measure of the psychological influence of the food environment. *Appetite.* 2009;53(1):114-118.

195. Dykens EM, Maxwell MA, Pantino E, Kossler R, Roof E. Assessment of hyperphagia in Prader-Willi syndrome. *Obesity (Silver Spring, Md.).* 2007;15(7):1816-1826.

196. Styne DM, Arslanian SA, Connor EL, et al. Pediatric Obesity-Assessment, Treatment, and Prevention: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2017;102(3):709-757.

197. Apovian CM, Aronne LJ, Bessesen DH, et al. Pharmacological management of obesity: an endocrine Society clinical practice guideline. *The Journal of clinical endocrinology and metabolism.* 2015;100(2):342-362.

198. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Circulation.* 2014;129(25 Suppl 2):S102-138.

199. Johnston BC, Kanters S, Bandayrel K, et al. Comparison of weight loss among named diet programs in overweight and obese adults: a meta-analysis. *JAMA.* 2014;312(9):923-933.

200. Parada M, Hernandez L, Schwartz D, Hoebel BG. Hypothalamic infusion of amphetamine increases serotonin, dopamine and norepinephrine. *Physiol Behav.* 1988;44(4-5):607-610.

201. Goldfield GS, Lorello C, Doucet E. Methylphenidate reduces energy intake and dietary fat intake in adults: a mechanism of reduced reinforcing value of food? *Am J Clin Nutr.* 2007;86(2):308-315.

202. Samanin R, Bendotti C, Bernasconi S, Borroni E, Garattini S. Role of brain monoamines in the anorectic activity of mazindol and d-amphetamine in the rat. *Eur J Pharmacol.* 1977;43(2):117-124.

203. Schweickert LA, Strober M, Moskowitz A. Efficacy of methylphenidate in bulimia nervosa comorbid with attention-deficit hyperactivity disorder: a case report. *The International journal of eating disorders.* 1997;21(3):299-301.

204. Sokol MS, Gray NS, Goldstein A, Kaye WH. Methylphenidate treatment for bulimia nervosa associated with a cluster B personality disorder. *The International journal of eating disorders.* 1999;25(2):233-237.

205. Garvey WT, Ryan DH, Look M, et al. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study. *The American journal of clinical nutrition.* 2012;95(2):297-308.

206. Allison DB, Gadde KM, Garvey WT, et al. Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP). *Obesity.* 2012;20(2):330-342.

207. McElroy SL, Hudson JI, Mitchell JE, et al. Efficacy and safety of lisdexamfetamine for treatment of adults with moderate to severe binge-eating disorder: a randomized clinical trial. *JAMA psychiatry.* 2015;72(3):235-246.

208. Kanoski SE, Hayes MR, Skibicka KP. GLP-1 and weight loss: unraveling the diverse neural circuitry. *Am J Physiol Regul Integr Comp Physiol.* 2016;310(10):R885-895.

209. Sohn JW, Xu Y, Jones JE, Wickman K, Williams KW, Elmquist JK. Serotonin 2C receptor activates a distinct population of arcuate pro-opiomelanocortin neurons via TRPC channels. *Neuron.* 2011;71(3):488-497.

210. Mashiko S, Moriya R, Ishihara A, et al. Synergistic interaction between neuropeptide Y1 and Y5 receptor pathways in regulation of energy homeostasis. *European journal of pharmacology.* 2009;615(1-3):113-117.

211. Adan RA. Mechanisms underlying current and future anti-obesity drugs. *Trends in neurosciences.* 2013;36(2):133-140.

212. Danielsson P, Janson A, Norgren S, Marcus C. Impact sibutramine therapy in children with hypothalamic obesity or obesity with aggravating syndromes. *J Clin Endocrinol Metab.* 2007;92(11):4101-4106.

213. Kang JG, Park CY. Anti-Obesity Drugs: A Review about Their Effects and Safety. *Diabetes & metabolism journal.* 2012;36(1):13-25.

214. Joharapurkar AA, Dhanesha NA, Jain MR. Inhibition of the methionine aminopeptidase 2 enzyme for the treatment of obesity. *Diabetes, metabolic syndrome and obesity.* 2014;7:73-84.

215. Elfers CT, Roth CL. Robust Reductions of Excess Weight and Hyperphagia by Beloranib in Rat Models of Genetic and Hypothalamic Obesity. *Endocrinology.* 2017;158(1):41-55.

216. McCandless SE, Yanovski JA, Miller J, et al. Effects of MetAP2 inhibition on hyperphagia and body weight in Prader-Willi syndrome: A randomized, double-blind, placebo-controlled trial. *Diabetes, obesity & metabolism.* 2017;19(12):1751-1761.

217. Malloy J, Clapper B, Zhuang D, et al. Single and Multiple Dose Evaluation of a Novel MetAP2 Inhibitor: Results of a Randomized, Double-Blind, Placebo-Controlled Clinical Trial. *Diabetes, obesity & metabolism.* 2018.

218. Munzberg H, Laque A, Yu S, Rezai-Zadeh K, Berthoud HR. Appetite and body weight regulation after bariatric surgery. *Obes Rev.* 2015;16 Suppl 1:77-90.

219. Bretault M, Boillot A, Muzard L, et al. Clinical review: Bariatric surgery following treatment for craniopharyngioma: a systematic review and individual-level data meta-analysis. *The Journal of clinical endocrinology and metabolism.* 2013;98(6):2239-2246.

220. Sjostrom L, Lindroos AK, Peltonen M, et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *The New England journal of medicine.* 2004;351(26):2683-2693.

221. Peterli R, Steinert RE, Woelnerhanssen B, et al. Metabolic and hormonal changes after laparoscopic Roux-en-Y gastric bypass and sleeve gastrectomy: a randomized, prospective trial. *Obesity surgery.* 2012;22(5):740-748.

222. Halpern CH, Tekriwal A, Santollo J, et al. Amelioration of binge eating by nucleus accumbens shell deep brain stimulation in mice involves D2 receptor modulation. *The Journal of neuroscience.* 2013;33(17):7122-7129.

223. Roth CL, Eslamy H, Werny D, et al. Semiquantitative analysis of hypothalamic damage on MRI predicts risk for hypothalamic obesity. *Obesity.* 2015;23(6):1226-1233.

224. Ogawa S, Lee TM, Kay AR, Tank DW. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proceedings of the National Academy of Sciences of the United States of America.* 1990;87(24):9868-9872.

225. Baroncini M, Jissendi P, Balland E, et al. MRI atlas of the human hypothalamus. *NeuroImage.* 2012;59(1):168-180.

226. Xu Y, Jones JE, Lauzon DA, et al. A serotonin and melanocortin circuit mediates D-fenfluramine anorexia. *J Neurosci.* 2010;30(44):14630-14634.

227. Burke LK, Heisler LK. 5-hydroxytryptamine medications for the treatment of obesity. *J Neuroendocrinol.* 2015;27(6):389-398.

228. Adan RA, Tiesjema B, Hillebrand JJ, la Fleur SE, Kas MJ, de Krom M. The MC4 receptor and control of appetite. *Br J Pharmacol.* 2006;149(7):815-827.

229. MacNeil DJ. NPY Y1 and Y5 receptor selective antagonists as anti-obesity drugs. *Curr Top Med Chem.* 2007;7(17):1721-1733.

230. Collet TH, Dubern B, Mokrosinski J, et al. Evaluation of a melanocortin-4 receptor (MC4R) agonist (Setmelanotide) in MC4R deficiency. *Molecular metabolism.* 2017;6(10):1321-1329.

231. van der Klaauw AA, Ziauddeen H, Keogh JM, et al. Oxytocin administration suppresses hypothalamic activation in response to visual food cues. *Scientific reports.* 2017;7(1):4266.

232. Lawson EA, Marengi DA, DeSanti RL, Holmes TM, Schoenfeld DA, Tolley CJ. Oxytocin reduces caloric intake in men. *Obesity.* 2015;23(5):950-956.

233. Ott V, Finlayson G, Lehnert H, et al. Oxytocin reduces reward-driven food intake in humans. *Diabetes.* 2013;62(10):3418-3425.

234. Kuppens RJ, Donze SH, Hokken-Koelega AC. Promising effects of oxytocin on social and food-related behaviour in young children with Prader-Willi syndrome: a randomized, double-blind, controlled crossover trial. *Clinical endocrinology.* 2016;85(6):979-987.

235. Miller JL, Tamura R, Butler MG, et al. Oxytocin treatment in children with Prader-Willi syndrome: A double-blind, placebo-controlled, crossover study. *American journal of medical genetics.* 2017;173(5):1243-1250.

236. Lee MR, Scheidweiler KB, Diao XX, et al. Oxytocin by intranasal and intravenous routes reaches the cerebrospinal fluid in rhesus macaques: determination using a novel oxytocin assay. *Molecular psychiatry.* 2018;23(1):115-122.

237. Carney CE, Buysse DJ, Ancoli-Israel S, et al. The consensus sleep diary: standardizing prospective sleep self-monitoring. *Sleep.* 2012;35(2):287-302.

238. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep.* 1991;14(6):540-545.

239. Johns MW. The assessment of sleepiness in children and adolescents. *Sleep Biol Rhytm.* 2015;13(Suppl 1):97.

240. Carskadon MA, Dement WC, Mitler MM, Roth T, Westbrook PR, Keenan S. Guidelines for the multiple sleep latency test (MSLT): a standard measure of sleepiness. *Sleep.* 1986;9(4):519-524.

241. Tachibana N, Taniike M, Okinaga T, Ripley B, Mignot E, Nishino S. Hypersomnolence and increased REM sleep with low cerebrospinal fluid hypocretin level in a patient after removal of craniopharyngioma. *Sleep medicine.* 2005;6(6):567-569.

242. Muller HL, Muller-Stover S, Gebhardt U, Kolb R, Sorensen N, Handwerker G. Secondary narcolepsy may be a causative factor of increased daytime sleepiness in obese childhood craniopharyngioma patients. *JPEM.* 2006;19 Suppl 1:423-429.

243. Marcus CL, Trescher WH, Halbower AC, Lutz J. Secondary narcolepsy in children with brain tumors. *Sleep.* 2002;25(4):435-439.

244. Epstein LJ, Kristo D, Strollo PJ, Jr., et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *Journal of clinical sleep medicine.* 2009;5(3):263-276.

245. Morgenthaler TI, Lee-Chiong T, Alessi C, et al. Practice parameters for the clinical evaluation and treatment of circadian rhythm sleep disorders. An American Academy of Sleep Medicine report. *Sleep.* 2007;30(11):1445-1459.

246. Morgenthaler TI, Owens J, Alessi C, et al. Practice parameters for behavioral treatment of bedtime problems and night wakings in infants and young children. *Sleep.* 2006;29(10):1277-1281.

247. Morgenthaler T, Kramer M, Alessi C, et al. Practice parameters for the psychological and behavioral treatment of insomnia: an update. An american academy of sleep medicine report. *Sleep.* 2006;29(11):1415-1419.

248. Brasure M, Fuchs E, MacDonald R, et al. Psychological and Behavioral Interventions for Managing Insomnia Disorder: An Evidence Report for a Clinical Practice Guideline by the American College of Physicians. *Annals of internal medicine.* 2016;165(2):113-124.

249. Auger RR, Burgess HJ, Emens JS, Deriy LV, Thomas SM, Sharkey KM. Clinical Practice Guideline for the Treatment of Intrinsic Circadian Rhythm Sleep-Wake Disorders: Advanced Sleep-Wake Phase Disorder (ASWPD), Delayed Sleep-Wake Phase Disorder (DSWPD), Non-24-Hour Sleep-Wake Rhythm Disorder (N24SWD), and Irregular Sleep-Wake Rhythm Disorder (ISWRD). An Update for 2015: An American Academy of Sleep Medicine Clinical Practice Guideline. *Journal of clinical sleep medicine.* 2015;11(10):1199-1236.

250. Morgenthaler TI, Kapur VK, Brown T, et al. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. *Sleep.* 2007;30(12):1705-1711.

251. Crowley RK, Woods C, Fleming M, et al. Somnolence in adult craniopharyngioma patients is a common, heterogeneous condition that is potentially treatable. *Clinical endocrinology.* 2011;74(6):750-755.

252. Rosen GM, Bendel AE, Neglia JP, Moertel CL, Mahowald M. Sleep in children with neoplasms of the central nervous system: case review of 14 children. *Pediatrics.* 2003;112(1 Pt 1):e46-54.

253. Marcus CL, Brooks LJ, Draper KA, et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics.* 2012;130(3):e714-755.

254. O'Gorman CS, Simoneau-Roy J, Pencharz P, et al. Sleep-disordered breathing is increased in obese adolescents with craniopharyngioma compared with obese controls. *The Journal of clinical endocrinology and metabolism.* 2010;95(5):2211-2218.

255. Muller HL, Handwerker G, Wollny B, Faldum A, Sorensen N. Melatonin secretion and increased daytime sleepiness in childhood craniopharyngioma patients. *J Clin Endocrinol Metab.* 2002;87(8):3993-3996.

256. Lipton J, Megerian JT, Kothare SV, et al. Melatonin deficiency and disrupted circadian rhythms in pediatric survivors of craniopharyngioma. *Neurology.* 2009;73(4):323-325.

257. Murata J, Sawamura Y, Ikeda J, Hashimoto S, Honma K. Twenty-four hour rhythm of melatonin in patients with a history of pineal and/or hypothalamo-neurohypophyseal germinoma. *Journal of pineal research.* 1998;25(3):159-166.

258. Joustra SD, Thijs RD, van den Berg R, et al. Alterations in diurnal rhythmicity in patients treated for nonfunctioning pituitary macroadenoma: a controlled study and literature review. *European journal of endocrinology.* 2014;171(2):217-228.

259. Aldrich MS, Naylor MW. Narcolepsy associated with lesions of the diencephalon. *Neurology.* 1989;39(11):1505-1508.

260. Schwartz WJ, Stakes JW, Hobson JA. Transient cataplexy after removal of a craniopharyngioma. *Neurology.* 1984;34(10):1372-1375.

261. Sakuta K, Nakamura M, Komada Y, et al. Possible mechanism of secondary narcolepsy with a long sleep time following surgery for craniopharyngioma. *Internal medicine (Tokyo, Japan).* 2012;51(4):413-417.

262. Laudon M, Frydman-Marom A. Therapeutic effects of melatonin receptor agonists on sleep and comorbid disorders. *International journal of molecular sciences.* 2014;15(9):15924-15950.

263. Carley DW, Prasad B, Reid KJ, et al. Pharmacotherapy of Apnea by Cannabimimetic Enhancement, the PACE Clinical Trial: Effects of Dronabinol in Obstructive Sleep Apnea. *Sleep*. 2018;41(1).

264. Westerterp KR. Assessment of physical activity: a critical appraisal. *European journal of applied physiology*. 2009;105(6):823-828.

265. Westerterp KR. Doubly labelled water assessment of energy expenditure: principle, practice, and promise. *European journal of applied physiology*. 2017;117(7):1277-1285.

266. Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. *Thyroid*. 2016;26(10):1343-1421.

267. van Marken Lichtenbelt WD, Vanhommerig JW, Smulders NM, et al. Cold-activated brown adipose tissue in healthy men. *The New England journal of medicine*. 2009;360(15):1500-1508.

268. Mukherjee J, Baranwal A, Schade KN. Classification of Therapeutic and Experimental Drugs for Brown Adipose Tissue Activation: Potential Treatment Strategies for Diabetes and Obesity. *Current diabetes reviews*. 2016;12(4):414-428.

269. Arch JR. beta(3)-Adrenoceptor agonists: potential, pitfalls and progress. *European journal of pharmacology*. 2002;440(2-3):99-107.

270. Cypess AM, Weiner LS, Roberts-Toler C, et al. Activation of human brown adipose tissue by a beta3-adrenergic receptor agonist. *Cell metabolism*. 2015;21(1):33-38.

271. Gadde KM, Yonish GM, Wagner HR, 2nd, Foust MS, Allison DB. Atomoxetine for weight reduction in obese women: a preliminary randomised controlled trial. *International journal of obesity (2005)*. 2006;30(7):1138-1142.

272. McElroy SL, Guerdjikova A, Kotwal R, et al. Atomoxetine in the treatment of binge-eating disorder: a randomized placebo-controlled trial. *The Journal of clinical psychiatry*. 2007;68(3):390-398.

273. Pott W, Albayrak O, Hinney A, Hebebrand J, Pauli-Pott U. Successful treatment with atomoxetine of an adolescent boy with attention deficit/hyperactivity disorder, extreme obesity, and reduced melanocortin 4 receptor function. *Obesity facts*. 2013;6(1):109-115.

274. Ohno H, Shinoda K, Spiegelman BM, Kajimura S. PPARgamma agonists induce a white-to-brown fat conversion through stabilization of PRDM16 protein. *Cell metabolism*. 2012;15(3):395-404.

275. Liu X, Zheng Z, Zhu X, et al. Brown adipose tissue transplantation improves whole-body energy metabolism. *Cell research*. 2013;23(6):851-854.

276. Gutch M, Kumar S, Razi SM, Gupta KK, Gupta A. Assessment of insulin sensitivity/resistance. *Indian journal of endocrinology and metabolism*. 2015;19(1):160-164.

277. Diagnosis and classification of diabetes mellitus. *Diabetes care*. 2014;37 Suppl 1:S81-90.

278. Ryden L, Grant PJ, Anker SD, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). *European heart journal*. 2013;34(39):3035-3087.

279. Handelsman Y, Bloomgarden ZT, Grunberger G, et al. American association of clinical endocrinologists and american college of endocrinology - clinical practice guidelines for developing a diabetes mellitus comprehensive care plan - 2015. *Endocrine practice*. 2015;21 Suppl 1:1-87.

280. Rosenzweig JL, Ferrannini E, Grundy SM, et al. Primary prevention of cardiovascular disease and type 2 diabetes in patients at metabolic risk: an endocrine society clinical practice guideline. *The Journal of clinical endocrinology and metabolism*. 2008;93(10):3671-3689.

281. Levy-Marchal C, Arslanian S, Cutfield W, et al. Insulin resistance in children: consensus, perspective, and future directions. *The Journal of clinical endocrinology and metabolism*. 2010;95(12):5189-5198.

282. Tzotzas T, Papazisis K, Perros P, Krassas GE. Use of somatostatin analogues in obesity. *Drugs*. 2008;68(14):1963-1973.

283. Astrup A, Rossner S, Van Gaal L, et al. Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. *Lancet (London, England).* 2009;374(9701):1606-1616.

284. Malin SK, Kashyap SR. Effects of metformin on weight loss: potential mechanisms. *Current opinion in endocrinology, diabetes, and obesity.* 2014;21(5):323-329.

285. Lv WS, Wen JP, Li L, et al. The effect of metformin on food intake and its potential role in hypothalamic regulation in obese diabetic rats. *Brain research.* 2012;1444:11-19.

286. Zambon A, Cusi K. The role of fenofibrate in clinical practice. *Diabetes & vascular disease research*. 2007;4 Suppl 3:S15-20.

287. Blundell J, Finlayson G, Axelsen M, et al. Effects of once-weekly semaglutide on appetite, energy intake, control of eating, food preference and body weight in subjects with obesity. *Diabetes, obesity & metabolism*. 2017;19(9):1242-1251.

288. O'Neil PM, Birkenfeld AL, McGowan B, et al. Efficacy and safety of Semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial. *Lancet*. 2018; 392(10148):637-649.

289. Fleseriu M, Hashim IA, Karavitaki N, et al. Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2016;101(11):3888-3921.

290. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. GH Research Society. *The Journal of clinical endocrinology and metabolism.* 2000;85(11):3990-3993.

291. Costin G, Kogut MD, Phillips LS, Daughaday WH. Craniopharyngioma: the role of insulin in promoting postoperative growth. *J Clin Endocrinol Metab.* 1976;42(2):370-379.

292. Chemaitilly W, Armstrong GT, Gajjar A, Hudson MM. Hypothalamic-Pituitary Axis Dysfunction in Survivors of Childhood CNS Tumors: Importance of Systematic Follow-Up and Early Endocrine Consultation. *Journal of clinical oncology.* 2016;34(36):4315-4319.

293. Karavitaki N, Warner JT, Marland A, et al. GH replacement does not increase the risk of recurrence in patients with craniopharyngioma. *Clinical endocrinology.* 2006;64(5):556-560.

294. Price DA, Wilton P, Jonsson P, et al. Efficacy and safety of growth hormone treatment in children with prior craniopharyngioma: an analysis of the Pharmacia and Upjohn International Growth Database (KIGS) from 1988 to 1996. *Hormone research.* 1998;49(2):91-97.

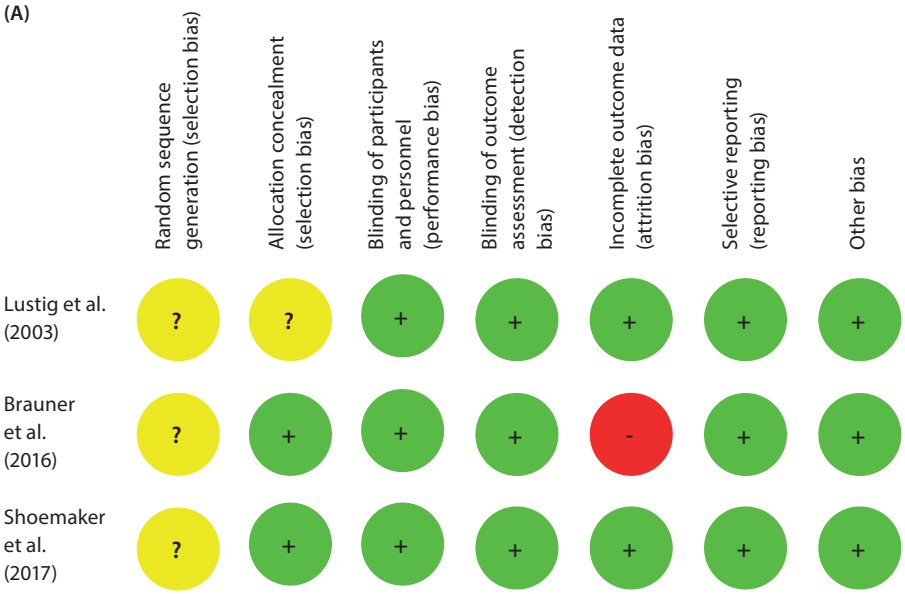
295. Olsson DS, Buchfelder M, Wiendieck K, et al. Tumour recurrence and enlargement in patients with craniopharyngioma with and without GH replacement therapy during more than 10 years of follow-up. *European journal of endocrinology.* 2012;166(6):1061-1068.

296. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2018;103(5):1715-1744.

297. Rose SR, Lustig RH, Pitukcheewanont P, et al. Diagnosis of hidden central hypothyroidism in survivors of childhood cancer. *J Clin Endocrinol Metab.* 1999;84(12):4472-4479.

Supplementary material

Supplemental Figure 1. Evaluation of methodological quality of randomized controlled studies using The Cochrane Risk of Bias tool. (a) Risk of bias summary for studies by Lustig et al. (2003), Brauner et al. (2016), and Shoemaker et al. (2017). (b) Bar graph of bias risk and type for the studies included in the systematic review



Supplemental Table 1. Search strategy

Source	N	Search Terms
Medline	835	((("Craniopharyngioma"[Mesh]) OR "hypothalamic obesity"[tiab]) OR "Hypothalamic Neoplasms/complications*" [MesH]) OR craniopharyngioma*[Title/Abstract])) AND ((((((((((((((((("Body Weight"[Mesh]) OR "Body Mass Index"[Mesh]) OR "Obesity"[Mesh]) OR bmi[Title/Abstract]) OR body weight[Title/Abstract]) OR overweight[Title/Abstract]) OR weight gain[Title/Abstract]) OR weight [Title/Abstract]) OR obes*[Title/Abstract]) OR body weights[Title/Abstract]) OR adiposity [Title/Abstract]) OR body fat [Title/Abstract]) OR body mass[Title/Abstract]) OR fat mass [Title/Abstract]) OR liveweight[Title/Abstract])) OR ((weight[Title/Abstract]) AND ((((((((((((increase*[Title/Abstract]) OR gain*[Title/Abstract]) OR increase* [Title/Abstract]) OR loss*[Title/Abstract]) impair*[Title/Abstract]) OR reduc*[Title/Abstract]) OR decreas*[Title/Abstract]) OR loosing[Title/Abstract]) OR fluctuat*[Title/Abstract]) OR chang*[Title/Abstract]) OR control*[Title/Abstract]) OR variat*[Title/Abstract]))))
EMBASE	1031	'body weight'/exp OR 'body weight' OR 'obesity'/exp OR 'obesity' OR 'body mass index'/exp OR 'body mass index' OR 'body weight':ab,ti OR 'overweight':ab,ti OR 'weight gain':ab,ti OR obes*:ab,ti OR 'body mass index':ab,ti OR 'body mass':ab,ti OR 'fat mass':ti,ab OR (live AND weight:ab,ti OR 'weight':ab,ti AND increase*:ab,ti) OR gain*:ab,ti OR loss*:ab,ti OR 'reduct*':ab,ti OR increase:ti,ab OR 'impairment':ab,ti OR 'loosing' OR 'fluctua*t':ab,ti OR 'chang*':ab,ti OR 'control*':ab,ti OR 'variat*':ab,ti AND (('craniopharyngeoma'/exp OR 'craniopharyngeoma') OR 'craniopharyngioma':ab,ti OR 'hypothalamic obesity':ab,ti OR 'hypothalamus tumor'/exp OR 'hypothalamus lesion'/exp) AND [embase]/lim NOT [medline]/lim

Supplemental Table 2. Evaluation of methodological quality of cohort studies using ROBINS-I*

*Summary of risk of bias.

Study Author (Year)	Confounding	Selection	Measurement of Intervention	Deviation from Intervention	Missing Data	Measurement of Outcomes	Reported Results	Overall
Geffner (2004)	Serious	Low	Low	Low	Moderate	Low	Low	Serious
Yuen (2013)	Serious	Low	Low	Low	Moderate	Low	Moderate	Serious
Weismann (2013)	Serious	Moderate	Moderate	Moderate	Low	Moderate	Serious	Serious
Sterkenburg (2014)	Serious	No information	Low	No information	Low	Low	Low	Serious
Wijnen (2017)	Serious	Low	Low	Low	Low	Low	Moderate	Serious

Supplemental Table 3. GRADE evidence and summary of findings

Certainty Assessment							Impact	Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsis-tency**	**Indirectness**	**Imprecision**	**Other considerations**		
Psychosocial, psychologic, and psychiatric disorders - Specialized outpatient clinic (follow up: range 0.97 years to 9 years)								
2 [1,2]	Observational studies	Very serious[a]	Serious[b]	Not serious	Very serious[c]	None	116 patients with intervention, no control patients. Weight gain decrease in one study, weight gain in the second study. However, in last study, 45.5% had no weight gain. Improvements in patient (but not in parent) reported quality of life and school functioning after visiting outpatient clinic.	⊕○○○ VERY LOW
Psychosocial, psychologic, and psychiatric disorders - Rehabilitation (follow up: range 8 weeks to 9 years)								
3 [3,4,5]	Observational studies	Very serious[a]	Serious[b]	Not serious	Very serious[c]	None	34 patients with intervention, 77 control patients. Failure to modify behavior after hospitalization in psychiatric hospital. Improvement of depressive symptoms after admittance to pediatric hospital. Weight gain was seen after hospital discharge (or during weekend in home environment). Patients who underwent rehabilitation still had a higher BMI after intervention, compared to patients without rehabilitation.	⊕○○○ VERY LOW

Psychosocial, psychological and psychiatric disorders - Stimulants (follow up: range 7 months to 63 months)								
2 [6,7]	Observational studies	Very serious[a]	Not serious	Not serious	Very serious[c]	Publication bias strongly suspected[d]	17 patients with intervention, no control patients. Significant improvements in overall activity, attention, daytime wakefulness, and/or concentration after dextroamphetamine. Patients experienced either stabilization of weight or weight loss.	⊕○○○ VERY LOW
Hyperphagia - Stimulants (follow up: range 24 months to 87 weeks)								
3 [6,8,9]	Observational studies	Very serious[a]	Very serious[b]	Not serious	Very serious[c]	Publication bias strongly suspected[e]	7 patients with intervention, no control patients. No difference in parent-reported food intake after dextroamphetamine, subjective decrease in hunger after methylphenidate, disappearance of hyperphagia after mazindol. Patients experienced either stabilization of weight or weight loss.	⊕○○○ VERY LOW
Hyperphagia - Antidiabetics (follow up: range 2 months to 4 years)								
6 [10,11,12,13,14,15]	Observational studies	Very serious[a]	Not serious	Not serious	Very serious[c]	Strong association	23 patients with intervention, no control patients. Anorexic effects after a combination with metformin and pioglitazone. However, fluctuations in weight, depending on the clinical course. All studies reported reduced appetite, cravings for food, and/or increased feelings of satiety after food ingestion after GLP-1 agonists, within most studies successful weight loss.	⊕○○○ VERY LOW

Hyperphagia - Bariatric surgery (follow up: range 18 months to 9.1 years)								
3 [16,17,18]	Observational studies	Very serious[a]	Very serious[b]	Not serious	Very serious[c]	Publication bias strongly suspected[f]	8 patients with intervention, no control patients. A decrease interest in food and/or craving was noted after LAGB and Roux-en-Y (RYGB) gastric bypass. One study revealed decreased food intake after the first postoperative month; however, this returned to preoperative food amounts 1 year after RYGB or sleeve gastrectomy. Long-term weight loss was not seen after LAGB. Weight reduction after SG and RYGB (however, no long-term follow-up data).	⊕○○○ VERY LOW
Daytime somnolence - Stimulants (follow up: range 13 months to 15 months)								
1 [7]	Observational studies	Very serious[a]	Very serious[g]	Not serious	Very serious[h]	None	12 patients with intervention, no control patients. All patients with daytime somnolence, reported subjective improvement in daytime wakefulness on treatment. Patients experienced either stabilization of weight or weight loss.	⊕○○○ VERY LOW
Energy expenditure - Stimulants (follow up: range 2 months to 63 months)								
4 [6,7,19,20]	Observational studies	Very serious[a]	Very serious[b]	Not serious	Very serious[c]	Publication bias strongly suspected[l]	21 patients with intervention, no control patients. Improvement in the activity or physical exercise tolerance after dextroamphetamine, together with either stabilization of weight or weight loss. Subjective improvement of energy level and weight after T3 in one study, but no effect of T3 on resting energy expenditure, brown adipose tissue and weight in other study.	⊕○○○ VERY LOW

Hyperinsulinemia - Antidiabetic agents (not including GLP-1 agonists) or somatostatin analogues (follow up: range 6 months to 30 months)								
6 [10,21,22,23,24,25]	Randomized controlled trials (n = 2) Observational studies (n = 4)	Very serious[j,k]	Very serious[b]	Not serious	Very serious[c]	None	69 patients with intervention, 27 control patients. In patients with poor glycemic control and/or hyperinsulinemia, improvements were seen in HOMA-IR, HbA1c, and/or insulin concentrations after antidiabetics. However, after diazoxide treatment, fasting and stimulated glucose concentrations increased, and three patients developed diabetes mellitus. In one study, stimulated glucose concentrations decreased after octreotide (with constant HbA1c levels), but in the RCT this result could not be validated. The effects of either antidiabetics and octreotide varied across different studies.	⊕○○○ VERY LOW
Hyperinsulinemia - GLP-1 agonists (follow up: range 2 months to 4 years)								
5 [11,12,13,14,15]	Observational studies	Very serious[a]	Serious[b]	Not serious	Very serious[c,h]	None	22 patients with intervention, no control patients. GLP-1 agonists improved glycemic control, and in general demonstrated successful weight loss, also in the patients that had good glycemic control before the start of the intervention.	⊕○○○ VERY LOW

Hypopituitarism - GH (follow up: range 3 years to 5 years)								
2 [26,27]	Observational studies	Very serious[l]	Serious[b]	Not serious	Very serious[h]	Publication bias strongly suspected [m]	459 patients with intervention, 722 control population. Weight stabilization was seen after GH therapy in children. In adults, BMI significantly increased in both males as females.	⊕○○○ VERY LOW

Abbreviations: CI, confidence interval

Explanations

[a] Uncontrolled observational studies

[b] Conflicting results between studies

[c] Small studies, only descriptive outcomes

[d] Conference abstracts are available, but no final full-text article published

[e] Other pharmacotherapeutic interventions of Stimulants published, but they did not include outcomes on hyperphagia

[f] Other results of bariatric surgery published but did not include outcomes on hyperphagia

[g] Only one study included

[h] Only descriptive outcomes

[i] Other pharmacotherapeutic interventions of Stimulants published, but they did not include outcomes on energy expenditure

[j] Attrition bias in RCT

[k] Selection bias in RCT

[l] Controlled study not adjusted for confounding factors

[m] Industry-sponsored cohorts

References

1. Steele CA, Cuthbertson DJ, MacFarlane IA, et al. Hypothalamic obesity: prevalence, associations and longitudinal trends in weight in a specialist adult neuroendocrine clinic. Eur J Endocrinol; 2013.

2. Rakhshani N, Jeffery AS, Schulte F, et al. Evaluation of a comprehensive care clinic model for children with brain tumor and risk for hypothalamic obesity. Obesity; 2010.

3. Skorzewska A, Lal S, Waserman J, Guyda H. Abnormal food-seeking behavior after surgery for craniopharyngioma. Neuropsychobiology; 1989.

4. Meijneke RW, Schouten-van Meeteren AY, de Boer NY, et al. Hypothalamic obesity after treatment for craniopharyngioma: the importance of the home environment. J Pediatr Endocrinol Metab; 2015.

5. Sterkenburg AS, Hoffmann A, Gebhardt U, et al. Childhood craniopharyngioma with hypothalamic obesity - no long-term weight reduction due to rehabilitation programs. Klin Padiatr; 2014.

6. Mason PW, Krawiecki N, Meacham LR. The use of dextroamphetamine to treat obesity and hyperphagia in children treated for craniopharyngioma. Arch Pediatr Adolesc Med; 2002.

7. Ismail D, O'Connell MA, Zacharin MR. Dexamphetamine use for management of obesity and hypersomnolence following hypothalamic injury. J Pediatr Endocrinol Metab; 2006.

8. Elfers CT, Roth CL. Effects of methylphenidate on weight gain and food intake in hypothalamic obesity. Endocrinol; 2011.

9. Sadatomo T, Sakoda K, Yamanaka M, et al. Mazindol administration improved hyperphagia after surgery for craniopharyngioma--case report. Neurol Med Chir; 2001.

10. Igaki N, Tanaka M, Goto T. Markedly improved glycemic control and enhanced insulin sensitivity in a patient with type 2 diabetes complicated by a suprasellar tumor treated with pioglitazone and metformin. Intern Med; 2005.

11. Simmons JH, Shoemaker AH, Roth CL. Treatment with glucagon-like Peptide-1 agonist exendin-4 in a patient with hypothalamic obesity secondary to intracranial tumor. Horm Res Paediatr; 2012.

12. Thondam SK, Cuthbertson DJ, Aditya BS, et al. A glucagon-like peptide-1 (GLP-1) receptor agonist in the treatment for hypothalamic obesity complicated by type 2 diabetes mellitus. Clin Endocrinol; 2012.

13. Castro-Dufourny I, Carrasco R, Pascual JM. Hypothalamic obesity after craniopharyngioma surgery: Treatment with a long acting glucagon like peptide 1 derivated. Endocrinol Diabetes Nutr; 2017.

14. Zoicas F, Droste M, Mayr B, et al. GLP-1 analogues as a new treatment option for hypothalamic obesity in adults: report of nine cases. Eur J Endocrinol; 2013.

15. Lomenick JP, Buchowski MS, Shoemaker AH. A 52-week pilot study of the effects of exenatide on body weight in patients with hypothalamic obesity. Obesity; 2016.

16. Muller HL, Gebhardt U, Maroske J, et al. Long-term follow-up of morbidly obese patients with childhood craniopharyngioma after laparoscopic adjustable gastric banding (LAGB). Klin Padiatr; 2011.

17. Inge TH, Pfluger P, Zeller M, et al. Gastric bypass surgery for treatment of hypothalamic obesity after craniopharyngioma therapy. Nat Clin Pract Endocrinol Metab; 2007.

18. Bretault M, Laroche S, Lacorte JM, et al. Postprandial GLP-1 Secretion After Bariatric Surgery in Three Cases of Severe Obesity Related to Craniopharyngiomas. Obes Surg; 2016.

19. Fernandes JK, Klein MJ, Ater JL, et al. Triiodothyronine supplementation for hypothalamic obesity. Metabolism; 2002.

20. van Santen HM, Schouten-Meeteren AY, Serlie M, et al. Effects of T3 treatment on brown adipose tissue and energy expenditure in a patient with craniopharyngioma and hypothalamic obesity. J Pediatr Endocrinol Metab; 2015.

21. Kalina MA, Wilczek M, Kalina-Faska B, et al. Carbohydrate-lipid profile and use of metformin with micronized fenofibrate in reducing metabolic consequences of craniopharyngioma treatment in children: single institution experience. J Pediatr Endocrinol Metab; 2015.

22. Hamilton JK, Conwell LS, Syme C, et al. Hypothalamic Obesity following Craniopharyngioma Surgery: Results of a Pilot Trial of Combined Diazoxide and Metformin Therapy. Int J Pediatr Endocrinol; 2011.

23. Brauner R, Serreau R, Souberbielle JC, et al. Diazoxide in Children with Obesity After Hypothalamic-Pituitary Lesions: A Randomized, Placebo-Controlled Trial. J Clin Endocrinol Metab; 2016.

24. Lustig RH, Hinds PS, Ringwald-Smith K, et al. Octreotide therapy of pediatric hypothalamic obesity: a double-blind, placebo-controlled trial. J Clin Endocrinol Metab; 2003.

25. Lustig RH, Rose SR, Burghen GA, et al. Hypothalamic obesity caused by cranial insult in children: altered glucose and insulin dynamics and reversal by a somatostatin agonist. J Pediatr; 1999.

26. Yuen KC, Koltowska-Haggstrom M, Cook DM, et al. Clinical characteristics and effects of GH replacement therapy in adults with childhood-onset craniopharyngioma compared with those in adults with other causes of childhood-onset hypothalamic-pituitary dysfunction. Eur J Endocrinol; 2013.

27. Geffner M, Lundberg M, Koltowska-Haggstrom M, et al. Changes in height, weight, and body mass index in children with craniopharyngioma after three years of growth hormone therapy: analysis of KIGS (Pfizer International Growth Database). J Clin Endocrinol Metab; 2004.

Supplemental Table 4. Determinants of strength of recommendation

Question 1: Should a specialized outpatient clinic vs. usual community care be considered for patients with craniopharyngioma or other suprasellar tumors with hypothalamic obesity?

Decision domain	Judgement	Reason for judgement	Subdomains
1. Certainty about balance of desirable and undesirable outcomes or burden	Yes	The desirable consequences are substantial (*i.e.*, higher possible reduction in hospitalization, improvement in expertise and care by multidisciplinary, specialized team and weight loss). The undesirable consequences, such as travel distance to a clinic are relatively minor.	Children and adults will likely benefit equally.
2. High or moderate evidence	No	⊕○○○ There is very low-quality evidence that supports beneficial effects of a specialized outpatient clinic on weight.	Two observational uncontrolled studies, in children (n=1), and children & adults (n=1) respectively, have been performed including a specialized outpatient clinic.
3. Certainty or similarity in values and preferences	Yes	Uncertainty: there is no empirical evidence regarding the relative value patients place on specialized vs. usual community care. From expert opinion, we experience that patients prefer specialized care because of the rarity of the disease.	In both children and adults, there is no empirical evidence, but we expect preferences for care may be similar.
4. Resource implications (benefits outweigh costs)	Yes	There are resources required to provide specialized outpatient care, but these are balanced by decreased resource needs as a result of decreased hospitalizations and net cost is well worth it given the desirable outcomes.	The costs for children may be slightly higher than for adults, due to transitioning into adulthood.
Overall strength of recommendation	Weak	We recommend that both children and adults with craniopharyngioma or other suprasellar tumors with hypothalamic obesity should visit specialized outpatient clinics.	
Evidence to recommendation synthesis	The moderate-to high confidence that the desirable consequences are substantial, and the undesirable consequences modest, together with balanced cost-benefits, in the absence of high quality evidence, suggests a weak recommendation.		

Question 2: Should rehabilitation or hospitalization vs. usual community care be considered for patients with craniopharyngioma or other suprasellar tumors with hypothalamic obesity?

Decision domain	Judgement	Reason for judgement	Subdomains
1. Certainty about balance of desirable and undesirable outcomes or burden	No	The desirable consequences are substantial (*i.e.* weight loss, providing individualized dietary and exercise advice and psychosocial support). The undesirable consequences, such as isolation from the social and home environment, are substantial.	For children, the undesirable consequences of isolation from parents and social environment, may be higher compared to adults.
2. High or moderate evidence	No	⊕○○○ There is very low-quality evidence that supports beneficial effects on weight during rehabilitation or hospitalization, and harmful effects (*i.e.*, weight regain) after hospitalization.	In children, three studies (*i.e.,* cohort-study, case report and case-series), have been performed including rehabilitation or hospitalization.
3. Certainty or similarity in values and preferences	No	Uncertainty: there is no empirical evidence regarding the relative value patients place on rehabilitation or hospitalization.	In both children and adults, there is no empirical evidence, but we expect children do generally not favor hospitalization.
4. Resource implications (benefits outweigh costs)	Yes	There are resources required to provide rehabilitation or hospitalization, and these may not outweigh the benefits, as weight gain is seen after hospitalization.	
Overall strength of recommendation	Weak	For children with craniopharyngioma or other suprasellar tumors with hypothalamic obesity, hospitalization should be discouraged to reduce weight, as rapid weight regain occurs after discharge.	
Evidence to recommendation synthesis	The moderate-to high confidence that the desirable and undesirable consequences are substantial, together with high costs, in the absence of high quality evidence for beneficial effects on weight (in the long-term), suggests a weak recommendation.		

Question 3: Should stimulants vs. no drug intervention be considered for patients with craniopharyngioma or other suprasellar tumors with hypothalamic obesity to target psychosocial problems?

Decision domain	Judgement	Reason for judgement	Subdomains
1. Certainty about balance of desirable and undesirable outcomes or burden	Yes	The desirable consequences are substantial (*i.e.*, improvement in overall behavior, attention, concentration, impulse control and weight loss). The undesirable consequences, such as the adverse effects of treatment (*i.e.*, headaches and insomnia after dextroamphetamines), have been reported in a minority of patients. In general, dextroamphetamines have addictive properties	For children, the desirable consequences (due to stricter school regimens), may be higher compared to adults. Abuses of dextroamphetamines may be higher in the adult population.
2. High or moderate evidence	No	⨁◯◯◯ There is very low-quality evidence that supports beneficial effects on psychosocial problems and weight after dextroamphetamine.	In children, one observational uncontrolled study has been performed including dextroamphetamine. In children & adults, one case series has been performed including dextroamphetamine.
3. Certainty or similarity in values and preferences	Yes	Uncertainty: there is no empirical evidence regarding the relative value patients place on use of stimulants. From expert opinion, we experience that patients and parents generally are in favor of trying stimulants in case of psychosocial/behavioral problems.	In both children and adults, there is no empirical evidence, but we expect preferences for stimulants may be similar.
4. Resource implications (benefits outweigh costs)	Yes	The costs of dextroamphetamine are relatively low.	
Overall strength of recommendation	Weak	We recommend that for children and adults with craniopharyngioma or other suprasellar tumors with hypothalamic obesity and psychosocial problems, dextroamphetamine may be considered.	
Evidence to recommendation synthesis	The moderate-to high confidence that the desirable consequences are substantial, and the undesirable consequences modest, together with low costs, in the absence of high quality evidence, suggests a weak recommendation.		

Question 4: Should stimulants vs. no drug intervention be considered for patients with craniopharyngioma or other suprasellar tumors with hypothalamic obesity to target hyperphagia?

Decision domain	Judgement	Reason for judgement	Subdomains
1. Certainty about balance of desirable and undesirable outcomes or burden	Yes	The desirable consequences are substantial (*i.e.*, decrease in hunger and weight loss). The undesirable consequences, such as the adverse effects of treatment (*i.e.*, headaches and insomnia after dextroamphetamines), have been reported in a minority of patients. In general, dextroamphetamines have addictive properties	For children, the desirable consequences (due to stricter school regimens), may be higher compared to adults. Abuses of dextroamphetamines may be higher in the adult population.
2. High or moderate evidence	No	⊕○○○ There is very low-quality evidence that supports beneficial effects on hyperphagia and weight after methylphenidate and mazindol. There is no evidence that supports beneficial effects on hyperphagia after dextroamphetamine.	In children, one observational uncontrolled study including dextroamphetamine and one case report have been performed including methylphenidate. In adults, one case report has been performed including mazindol (currently withdrawn from the market).
3. Certainty or similarity in values and preferences	Yes	Uncertainty: there is no empirical evidence regarding the relative value patients place on use of stimulants. From expert opinion, we experience that patients and parents generally are in favor of trying stimulants in case of hyperphagia.	In both children and adults, there is no empirical evidence, but we expect preferences for stimulants may be similar.
4. Resource implications (benefits outweigh costs)	Yes	The costs of methylphenidate are relatively low.	
Overall strength of recommendation	Weak	We recommend that for children with craniopharyngioma or other suprasellar tumors with hypothalamic obesity and hyperphagia, methylphenidate may be considered. This recommendation is further supported by clinical studies and expert opinion.	
Evidence to recommendation synthesis	The moderate-to high confidence that the desirable consequences are substantial, and the undesirable consequences modest, together with low costs, in the absence of high quality evidence, suggests a weak recommendation.		

Question 5: Should antidiabetics vs. no drug intervention be considered for patients with craniopharyngioma or other suprasellar tumors with hypothalamic obesity to target hyperphagia?

Decision domain	Judgement	Reason for judgement	Subdomains
1. Certainty about balance of desirable and undesirable outcomes or burden	Yes	The desirable consequences are substantial (*i.e.*, reduced appetite, cravings for food and increased feelings of satiety and weight loss). The undesirable consequences, such as the adverse effects nausea and vomiting have been reported frequently after the use of GLP-1 agonists. Joint pain, injection site reactions increased irritability and mood swings or kidney stones have been reported in a minority of patients after GLP-1 agonists. GLP-1 administration may also require daily subcutaneous injections.	Children and adults will likely benefit equally. Children may experience more undesirable consequences, due to daily subcutaneous injections in case of GLP-1 agonists.
2. High or moderate evidence	No	⊕○○○ There is very low-quality evidence that supports beneficial effects on hyperphagia and weight after GLP-1 agonists. There is no evidence that supports beneficial effects on hyperphagia after combined use of metformin and pioglitazone.	In children, no study has been performed including GLP-1 or combined use of metformin and pioglitazone. In adults, five studies (*i.e.*, three case-reports, two uncontrolled observational studies) have been performed including GLP-1 agonists. One case-report has been performed including combined use of metformin and pioglitazone.
3. Certainty or similarity in values and preferences	No	Uncertainty: there is no empirical evidence regarding the relative value patients place on use of antidiabetics.	In both children and adults, there is no empirical evidence, but we expect children do generally not favor subcutaneous injections with GLP-1 agonists.
4. Resource implications (benefits outweigh costs)	No	The costs of GLP-1 agonists are relatively high.	

Overall strength of recommendation	Weak	We recommend that for adults with craniopharyngioma or other suprasellar tumors with hypothalamic obesity and hyperphagia, GLP-1 agonists may be considered. GLP-1 agonists should be considered in the context of an ethically-approved research study, if they have not been approved by the FDA or EMA.
Evidence to recommendation synthesis	The moderate-to high confidence that the desirable consequences are substantial, and may outweigh the undesirable consequences, in the absence of high quality evidence, suggests a weak recommendation.	

Question 6: Should bariatric surgery vs. no surgical intervention be considered for patients with craniopharyngioma or other suprasellar tumors with morbid hypothalamic obesity to target hyperphagia?

Decision domain	Judgement	Reason for judgement	Subdomains
1. Certainty about balance of desirable and undesirable outcomes or burden	Yes	The desirable consequences are substantial (i.e., reduced appetite and rapid and significant weight loss). The undesirable consequences, such as post-operative complications (including risk of adrenal crisis and hyper- or hyponatremia), vomiting dumping-type syndrome, re-surgery, and malabsorption of vitamins are severe.	Patients with the highest BMI, may experience more adverse effects (e.g., immobility prior or after surgery).
2. High or moderate evidence	No	⊕○○○ There is very low-quality evidence that supports beneficial effects on hyperphagia and weight after SG and RYGB. There is no evidence that supports beneficial effects on hyperphagia and weight after LAGB in the long term.	One study (case series) included two children (youngest 13.8 years) and two adults after LAGB. One study (case report) included an adult (18 years) after RYGB. One study (case series) included three adults (youngest 19 years) after RYGB and SG.
3. Certainty or similarity in values and preferences	No	Uncertainty: there is no empirical evidence regarding the relative value patients place on use of bariatric surgical procedures.	In children, bariatric surgeries, should be considered in exceptional cases.

4. Resource implications (benefits outweigh costs)	No	The costs of bariatric surgeries are high (varies highly between procedure, hospital and country), but these are balanced by decreased resource needs (e.g., health care costs) and higher productivity.
Overall strength of recommendation	Weak	We recommend that for adults with craniopharyngioma or other suprasellar tumors with morbid hypothalamic obesity and hyperphagia, bariatric surgical procedures may be considered.
Evidence to recommendation synthesis	The moderate-to high confidence that the desirable consequences are substantial, and may outweigh the undesirable consequences, in the absence of high quality evidence, suggests a weak recommendation.	

Question 7: Should stimulants vs. no drug intervention be considered for patients with craniopharyngioma or other suprasellar tumors with hypothalamic obesity to target daytime somnolence?

Decision domain	Judgement	Reason for judgement	Subdomains
1. Certainty about balance of desirable and undesirable outcomes or burden	Yes	The desirable consequences are substantial (*i.e.*, reduction of daytime somnolence, improvement of an active lifestyle and weight loss). The undesirable consequences, such as the adverse effects of treatment (*i.e.*, headaches and insomnia after dextroamphetamines), have been reported in a minority of patients. In general, dextroamphetamines have addictive properties	Children and adults will likely benefit equally. Abuses of dextroamphetamines may be higher in the adult population
2. High or moderate evidence	No	⊕○○○ There is very low-quality evidence that supports beneficial effects on daytime somnolence and weight after dextroamphetamine.	Only one study, including both children and adults assessed daytime somnolence and weight loss.
3. Certainty or similarity in values and preferences	No	Uncertainty: there is no empirical evidence regarding the relative value patients place on use of stimulants. From expert opinion, we experience that patients and parents generally are in favor of trying stimulants in case of daytime somnolence.	In both children and adults, there is no empirical evidence, but we expect preferences for stimulants may be similar.

4. Resource implications (benefits outweigh costs)	Yes	The costs of dextroamphetamine are relatively low.
Overall strength of recommendation	Weak	We recommend that for children and adults with craniopharyngioma or other suprasellar tumors with hypothalamic obesity and daytime somnolence, dextroamphetamine may be considered. This recommendation is further supported by existing guidelines and clinical studies that did not report on BMI as primary or secondary outcome.
Evidence to recommendation synthesis	The moderate-to high confidence that the desirable consequences are substantial, and the undesirable consequences modest, together with low costs, in the absence of high quality evidence, suggests a weak recommendation.	

Question 8: Should stimulants vs. no drug intervention be considered for patients with craniopharyngioma or other suprasellar tumors with hypothalamic obesity to target energy expenditure?

Decision domain	Judgement	Reason for judgement	Subdomains
1. Certainty about balance of desirable and undesirable outcomes or burden	Yes	The desirable consequences are substantial (*i.e.*, improved daily physical activity and weight loss). The undesirable consequences, such as the adverse effects of treatment (*i.e.*, headaches and insomnia after dextroamphetamines), have been reported in a minority of patients. In general, dextroamphetamines have addictive properties	Children and adults will likely benefit equally. Abuses of dextroamphetamines may be higher in the adult population
2. High or moderate evidence	No	⊕○○○ There is very low-quality evidence that supports beneficial effects on energy expenditure and weight after dextroamphetamine. There is no evidence that supports beneficial effects on energy expenditure and weight after supraphysiological T3 supplementation.	In children, one observational uncontrolled study including dextroamphetamine and one case report including supraphysiologic T3 supplementation have been performed. In children & adults, one case series has been performed including dextroamphetamine and one case series that assessed supraphysiologic T3 supplementation.

3. Certainty or similarity in values and preferences	No	Uncertainty: there is no empirical evidence regarding the relative value patients place on use of stimulants. From expert opinion, we experience that patients and parents generally are in favor of trying stimulants to increase energy expenditure.	In both children and adults, there is no empirical evidence, but we expect preferences for stimulants may be similar.
4. Resource implications (benefits outweigh costs)	Yes	The costs of dextroamphetamine are relatively low.	
Overall strength of recommendation	Weak	We recommend that for children and adults with craniopharyngioma or other suprasellar tumors with hypothalamic obesity and decreased energy expenditure, dextroamphetamine may be considered.	
Evidence to recommendation synthesis	The moderate-to high confidence that the desirable consequences are substantial, and the undesirable consequences modest, together with low costs, in the absence of high quality evidence, suggests a weak recommendation.		

Question 9: Should antidiabetics (excluding GLP-1 agonists) or somatostatin analogues vs. no drug intervention be considered for patients with craniopharyngioma or other suprasellar tumors with hypothalamic obesity to target hyperinsulinemia?

Decision domain	Judgement	Reason for judgement	Subdomains
1. Certainty about balance of desirable and undesirable outcomes or burden	No	The desirable consequences are substantial (*i.e.*, improved parameters of glucose homeostasis and weight loss). The undesirable consequences, such as the adverse effects of treatment, especially the occurrence of diabetes mellitus, edema and hirsutism after diazoxide, have been reported frequently after the use of diazoxide. Pedal edema, mildly elevated hepatic enzyme levels and vomiting have been reported in a minority of patients after combined metformin and diazoxide use.	Children and adults may experience both equally the undesirable consequences. Patients with higher insulin levels at baseline, may benefit more from antidiabetic therapy.

2. High or moderate evidence	No	⊕○○○ There is contradicting evidence that supports beneficial effects on hyperinsulinemia and weight after anti-diabetics. There is contradicting evidence that supports beneficial effects on hyperinsulinemia and weight after octreotide. There is very low-quality evidence that supports harmful effects (*i.e.*, occurrence of diabetes mellitus) after diazoxide use.	In children, one placebo-controlled study including octreotide (not approved as anti-obesity agent), and three uncontrolled observational studies including combined diazoxide and metformin, combined metformin and micronized fenofibrate, and octreotide One study including treatment with diazoxide was performed in children & adults. In adults, one case report has been performed including pioglitazone and metformin.
3. Certainty or similarity in values and preferences	Yes	Uncertainty: there is no empirical evidence regarding the relative value patients place on use of antidiabetics.	In both children and adults, there is no empirical evidence, but we expect preferences for antidiabetics may be similar.
4. Resource implications (benefits outweigh costs)	Yes	The costs of antidiabetics are relatively low, but the prices of somatostatin analogues may be higher.	
Overall strength of recommendation	Weak	For children and adults with CP or other suprasellar tumors with HO and hyperinsulinemia, the use of diazoxide is discouraged because of increased risk for hyperglycemia and diabetes mellitus.	
Evidence to recommendation synthesis	The moderate-to high confidence that the undesirable consequences are substantial, in the absence of high quality evidence for beneficial effects on weight, suggests a weak recommendation.		

Question 10: Should GLP-1 agonists vs. no drug intervention be considered for patients with craniopharyngioma or other suprasellar tumors with hypothalamic obesity to target hyperinsulinemia?

Decision domain	Judgement	Reason for judgement	Subdomains
1. Certainty about balance of desirable and undesirable outcomes or burden	Yes	The desirable consequences are substantial (i.e., reduced appetite, cravings for food and increased feelings of satiety and weight loss). The undesirable consequences, such as the adverse effects nausea and vomiting have been reported frequently after the use of GLP-1 agonists. Joint pain, injection site reactions increased irritability and mood swings or kidney stones have been reported in a minority of patients after GLP-1 agonists. GLP-1 administration may also require daily subcutaneous injections.	Children may experience more undesirable consequences, due to daily subcutaneous injections in case of GLP-1 agonists.
2. High or moderate evidence	No	⊕◯◯◯ There is very low-quality evidence that supports beneficial effects on hyperinsulinemia and weight after GLP-1 agonists.	In children, no study has been performed including GLP-1 agonists. In adults, five studies (*i.e.*, three case-reports, two uncontrolled observational studies) have been performed including GLP-1 agonists.
3. Certainty or similarity in values and preferences	No	Uncertainty: there is no empirical evidence regarding the relative value patients place on use of GLP-1 agonists.	In both children and adults, there is no empirical evidence, but we expect children do generally not favor subcutaneous injections with GLP-1 agonists.
4. Resource implications (benefits outweigh costs)	No	The costs of GLP-1 agonists are relatively high.	
Overall strength of recommendation	Weak	We recommend that in adults with craniopharyngioma or other suprasellar tumors with hypothalamic obesity and hyperinsulinemia, GLP-1 agonists may be considered. GLP-1 agonists should only be considered in the context of an ethically-approved research study, if they have not been approved by the FDA or EMA.	
Evidence to recommendation synthesis	The moderate-to high confidence that the desirable consequences are substantial, and may outweigh the undesirable consequences, in the absence of high quality evidence, suggests a weak recommendation.		

Question 11: Should GH therapy vs. no drug intervention be considered for patients with craniopharyngioma or other suprasellar tumors with hypothalamic obesity and GH deficiency?

Decision domain	Judgement	Reason for judgement	Subdomains
1. Certainty about balance of desirable and undesirable outcomes or burden	Yes	The desirable consequences are substantial (*i.e.*, improved final height, improved body composition and weight loss). In craniopharyngioma patients, studies do not suggest that GH therapy increases the risk of recurrence. Other undesirable outcomes, may be adverse effects (*e.g.*, muscle pain, edema, diabetes or slipped capital femoral epiphysis and daily subcutaneous injections), and are associated with GH therapy in general.	Children may experience more desirable consequences, because GH treatment can improve their final height.
2. High or moderate evidence	No	⨁◯◯◯ There is very low-quality evidence that supports beneficial effects on weight after GH therapy in children. There is no evidence that supports beneficial effects on weight after GH therapy in adults.	In children, one retrospective cohort study has been performed including GH therapy. In adults, one retrospective cohort study has been performed including GH therapy.
3. Certainty or similarity in values and preferences	No	Uncertainty: there is no empirical evidence regarding the relative value patients place on use of GH therapy.	In both children and adults, there is no empirical evidence, but we expect children do generally not favor subcutaneous injections.
4. Resource implications (benefits outweigh costs)	No	The costs of GH therapy are relatively high.	
Overall strength of recommendation	Weak	We recommend that for children with craniopharyngioma or other suprasellar tumors with hypothalamic obesity and GH deficiency, GH therapy may be considered.	
Evidence to recommendation synthesis	The moderate-to high confidence that the desirable consequences are substantial, and may outweigh the undesirable consequences, in the absence of high quality evidence, suggests a weak recommendation.		

4

Feasibility and effectiveness of an individualized dietary intervention for children with acquired hypothalamic obesity: a pilot study

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Submitted

Abstract

Objective

Studies targeting eating behavior in children with hypothalamic obesity (HO) following suprasellar tumors are lacking. This pilot study aimed to evaluate feasibility and effectiveness of an individualized dietary intervention.

Design

Prospective, one-year pilot study.

Methods

Participants with acquired HO, aged 6-18 years, received an individualized dietary plan (based on 7-8 kcal/cm height), and psychosocial support from a coach. Feasibility was assessed through recruitment, adherence and completion of the intervention. Effectiveness was defined as stabilization or reduction in BMI standard deviation score (SDS) in ≥80% of participants after one year. Interviews were conducted with participants and parents to evaluate the intervention.

Results

Six participants, median age 14.0 years (range, 11.8-17.1) were enrolled in the study. Dietary intake was reported for a median of 80.5 days (range, 13-290). Participants completed baseline and all follow-up visits. After 9 months, BMI SDS significantly decreased compared to baseline (median BMI SDS 2.47 vs 2.63 SDS, P=0.04). At 12 months, however, overall BMI SDS was similar compared to baseline, although two participants demonstrated BMI reduction (-0.19 and -0.14 SDS, respectively). Increased insight into individual energy requirements, nutrition knowledge, and support from the coach were experienced as positive by both participants and parents. The daily self-report of dietary intake was considered time- and energy consuming.

Conclusions

Individualized dietary intervention with extensive coaching improves insight into dietary requirements and is able to reduce BMI SDS in some children with acquired HO following suprasellar tumors. This study provides new strategies how long-term adherence and effectiveness may be improved.

Introduction

Craniopharyngioma and other suprasellar tumors are known to cause severe morbidity due to tumor- or treatment related damage of the pituitary gland, hypothalamus and other adjacent tissues.[1] Hypothalamic obesity (HO) is a common sequela in children with suprasellar tumors and results in impaired general health with excess morbidity and mortality.[2-4] In addition, quality of life (QoL), including domains of physical, cognitive, emotional and social functioning, is negatively affected by HO.[5-7]

HO is primarily the consequence of damage to the ventromedial hypothalamus and arcuate nucleus; two hypothalamic nuclei that play an important role in feelings of hunger, satiety, and the energy balance in general.[8] When these nuclei are damaged, proper integration of central and peripheral hormones is disrupted, which results in hyperphagia and excessive caloric intake.[9,10] Other sequelae observed following hypothalamic injury, such as decreased energy expenditure, hypopituitarism, hyperinsulinemia, psychosocial disorders and sleeping disturbances, may also contribute to development of HO.[11-13]

No overall effective treatment strategies are currently available for acquired HO, as this form of obesity seems resistant to pharmacological and non-pharmacological interventions.[14] Comprehensive lifestyle modifications, including dietary modification, are the starting point for antiobesity treatment in children from the general population.[15] However, the feasibility and effectiveness of dietary interventions for HO are questioned, as hyperphagia may limit adherence to dietary plans and the multifactorial causation of HO may induce only limited weight loss after restricting energy intake.[16] Importantly, prospective studies that specifically target eating patterns in children with HO following suprasellar tumors are currently lacking.[12] Therefore, the aim of this pilot study was to assess the feasibility and one-year effectiveness of an individualized dietary intervention in children with acquired HO.

Methods

Participant selection and eligibility

Children treated for craniopharyngioma or another suprasellar tumor, aged between 6-18 years, with a body mass index (BMI) >1.9 standard deviation score (SDS) and currently followed in our pediatric endocrinology outpatient clinic (Wilhelmina Children's Hospital, University Medical Center Utrecht), were eligible for this study. Participants had stable disease or no evidence of disease for >1 year. Children and parents provided written informed consent prior to enrollment.

Intervention

All participants received an individualized dietary plan for one year, with a follow-up visit three months after completion of the intervention.[17] The dietary plan consisted of an estimated energy need for each participant defined by a dietician and was based on the children's height (*i.e.* 7-8 kilocalories (kcal) per centimeter body height). This approach was used according to our best clinical practice and experiences with children with Prader-Willi syndrome, a genetic condition associated with HO.[18] The individual energy need was visualized for each participant by a corresponding number of dots; each dot representing 25 kcal. A number of dots was allocated to all food products depending on their nutritional composition. In addition, healthy food products were illustrated as green dots, and less healthy products as orange dots. There was no restriction on the types of food that participants were allowed to eat. Participants had to report when and what food products they had consumed on their individualized online platforms (www.happyweightstippenplan.nl) on a daily basis. The reported dots were also used to obtain insight in the dietary adherence of each participant. Every week, participants were encouraged to report online their home-measured weight as well.

A multidisciplinary team consisting of a dietician, (family) coach and pediatric endocrinologist was involved in the study. Participants visited their pediatric endocrinologist every three months in the outpatient endocrine clinic. Additionally, at baseline, after 3, 6 and 12 months, participants were seen by the dietician and coach. In between these visits, the dietician contacted the participants every month via telephone or email. The coach planned weekly contact via phone, text messaging, email or home visits with the participants and/or parents. The number of contacts could be individualized based on the participants' preferences. The coach was available for support throughout the entire study and provided education, feedback on eating habits, and recommendations specific to the participants' and parents' needs, preferences, and social environment. Although this intervention primarily focused on participants, the extent of parental involvement during the study was based on individual preferences and needs of participants and parents (e.g. separate parent counselling sessions during visits, phone calls). At completion of the study, interviews with participants and parents were conducted to evaluate experiences of intervention participation. This study protocol was approved by the Medical Research Ethics Committee of the University Medical Center Utrecht (Protocol number NL54980.041.15).

Criteria for feasibility and effectiveness

Recruitment feasibility was determined by the percentage of children recruited among those who were eligible and approached. The recruitment was considered successful if >70% of approached children could be enrolled in the study as participant. Intervention feasibility was assessed through adherence to (i.e. dietary intake by self-report) and completion of the intervention (>80% of participants). The intervention would meet the criteria for effectiveness if ≥80% of participants

showed BMI stabilization or reduction after the 1-year intervention. Secondary outcomes for assessment of effectiveness included changes in energy intake, metabolic outcomes, QoL and physical activity.

Study measurements

Weight and height; At every outpatient visit, weight and height were measured using a stadiometer and a digital scale, respectively. Body mass index (BMI) was calculated as weight in kilograms/(height in meters^2) and converted into age and gender adjusted SDS using the 2010 Dutch weight and height references.[19]

Energy intake; Participants completed a 5-day food record at baseline and at the 12-month follow-up visit. Food records were allocated in the week before the first and last outpatient visit. These records were used to calculate the average amount of energy intake per day at start and completion of the intervention. In addition, the types and amounts of specific products were compared to the Dutch dietary guidelines 2015.[20]

Metabolic outcomes; Metabolic outcomes included waist and hip circumferences as obtained by placing measuring tape horizontally at the level of the umbilicus or at the maximum circumference over the buttocks, respectively. A blood pressure was measured at baseline and all follow-up visits by trained staff. A blood specimen to check hormonal concentrations (IGF-1, FT4, TSH, LH, FSH, testosterone and estradiol, if applicable) was collected at every outpatient visit. In addition, fasting laboratory studies were obtained at baseline and at the 12-month follow-up visit, and included lipids, hemoglobin A1c (HbA1c) and a two-hour oral glucose tolerance testing (OGTT). Body composition was assessed using multifrequency bioelectrical impedance analysis (BIA, Bodystat Quadscan 4000, EuroMedix, Leuven, Belgium) at baseline and at completion of the study.

QoL; Participants and parents completed the age-appropriate versions of the Pediatric Quality of Life Inventory (PedsQL) (version 4.0) at every outpatient visit.[21] Participants and parents rated their functioning on a 5-point scale for physical (8 items), emotional (5 items), social (5 items) and school (5 items) domains. Questionnaires were reverse scored, ranging from 0 to 100 where higher scores indicate better QoL for each of the four domains. Two summary scores were calculated; the total scale score including all domains and the psychosocial health summary score, comprising the emotional, social and school functioning domains.

Physical activity; All participants were asked to complete the Habitual Activity Estimation Scale (HAES) questionnaire (version 1.6) at baseline, and at the 6 and 12-month follow-up visits for a typical weekday (either Tuesday, Wednesday or Thursday), and Saturday within the past week.[22] Participants reported their wakeup, bed, and meal times, and subsequently calculated the total

number of minutes per day spent in each of the four activity categories: inactive, somewhat inactive, somewhat active, and very active.

Intervention evaluation; Experiences of intervention participation were assessed during interviews with participants and parents post-intervention using paper questionnaires. The questionnaire included items about intervention satisfaction, suggestions for improvement of the intervention, and willingness to recommend the intervention to others.

Statistical analysis

Data are presented as median (range) for continuous data, or N (proportion in %) for categorical variables. Descriptive statistics are used to report characteristics of study participants, measurements of feasibility and intervention evaluation. Wilcoxon signed-rank tests were used for paired analyses to assess differences for total energy intake, metabolic outcomes (i.e. fat mass, waist- and hip circumferences), physical activity and QoL between baseline and the 12-month follow-up visit. Differences for BMI SDS were compared between baseline, over the course and at completion of the study. PedsQL values are reported as mean ± SD in order to compare study measurements with normative values from the general population using one-sample t-tests.[23,24] Significance levels for all analyses were set at $P < 0.05$.

Results

Study participants

Of the 11 participants screened for eligibility, six were eligible and approached to participate in this study. All six participants (100%) agreed to enroll. The median age of the participants at study was 14.0 years (range, 11.8-17.1), and four participants (66.7%) were female (Table 1). Four participants had a history of craniopharyngioma, one had suprasellar germinoma and one suprasellar pilocytic astrocytoma. All participants had been diagnosed with growth hormone (GH) deficiency, central hypothyroidism and central hypocortisolism, for which they received hormone replacement therapy. One female participant had spontaneous pubertal development, and the other five participants experienced hypogonadotropic hypogonadism, of whom two received estrogen or testosterone replacement therapy, respectively. Five participants had diabetes insipidus and one participant the syndrome of inappropriate antidiuretic hormone secretion. Two participants already experienced obesity (*i.e.* BMI SDS > 2) at diagnosis of their suprasellar tumor, and had acanthosis nigricans at start of the intervention. Two participants used dexamphetamine at start of the dietary intervention, which was initiated several years prior to this study.

Table 1. Socio-demographic characteristics of study participants

Participant	Gender	Age at diagnosis	Age at study	Time since diagnosis	Histology	Neuro-surgery	Radio-therapy, dose	Chemo-therapy	BMI (SDS) at diagnosis	BMI (SDS) at start study	Endocrine deficiencies
1.[6]	Female	10.7	17.1	6.4	CP	Yes	No	No	0.61	3.07	GHD, TSHD, ACTHD, LH/FSHD, DI
2.	Female	8.2	14.0	5.9	Germinoma	No	Yes, 24 Gy	Yes[2]	-0.27	2.18	GHD, TSHD, ACTHD, DI
3.[7]	Male	9.1	16.4	7.3	CP	Yes	Yes, 54 Gy	Yes[3]	0.87	1.91	GHD, TSHD, ACTHD, LH/FSHD, DI
4.[8]	Female	5.7	12.6	6.9	CP	Yes	No	No	5.12	5.10	GHD, TSHD, ACTHD, DI, LH/FSHD[5]
5.	Male	10.0	14.0	3.9	Pilocytic astrocytoma	Yes[1]	Yes, 54 Gy	Yes[4]	-1.18	1.58	GHD, TSHD, ACTHD, LH/FSHD[5], SIADH
6.	Female	5.6	11.8	6.2	CP	Yes	Yes, 54 Gy	No	3.04	4.44	GHD, TSHD, ACTHD, LH/FSHD[5], DI
Median, years (Range)	n.a.	8.6 (5.6-10.7)	14.0 (11.8-17.1)	6.3 (3.9-7.3)	n.a.	n.a.	n.a.	n.a.	0.74 (-1.18-5.12)	2.63 (1.58-5.10)	n.a.

[1] Participant has also received multiple neurosurgical procedures for moyamoya disease after initial tumor surgery
[2] Received chemotherapy according to SIOP CNS GCT II protocol
[3] Received intra-cystic Interferon-alpha therapy
[4] Received chemotherapy according to LGG 2004 protocol
[5] Participants were not (yet) on hormone replacement therapy for LH/FSHD
[6] Participant was already on dexamphetamine and melatonin prior to the intervention
[7] Participant had visual impairment
[8] Participant was already on dexamphetamine prior to the intervention
Abbreviations: ACTHD, adrenocorticotropic hormone deficiency; CP, craniopharyngioma; Gy, gray; DI, diabetes insipidus; GHD, growth hormone deficiency; LH/FSHD, luteinizing hormone/follicle-stimulating hormone deficiencies; SDS, standard deviation score; SIADH, syndrome of inappropriate antidiuretic hormone; TSHD, thyroid-stimulation hormone deficiency

Measurements of intervention feasibility

All six participants completed baseline and all follow-up outpatient visits. During the 1-year intervention, participants filled in their daily dietary intake for 290, 122, 13, 165, 18 and 39 days, respectively (median 80.5, range 13-290). The three participants who filled in their intake for > 100 days, reported in 11.7%, 21.3% and 15.2% of the days exactly the same dots as recommended, and in 71.0%, 66.4% and 75.2% of all days less than the advised daily intake (median -275, -200 and -350 kcal, respectively). Of the total products reported, 21.7%, 24.0% and 14.7% comprised of less healthy choices (*i.e.* orange dots). The coach had or attempted contacts with either the participants, their parents or other individuals involved in the care of participants for median 22 (range 5-58) times per participant during the study.

Effectiveness

BMI SDS

Changes in BMI SDS before, during and at the end of the 1-year intervention period are provided in Figure 1 and Table 2. Overall, the median BMI SDS at start of the intervention was 2.63 (range, 1.58-5.10), and did not significantly differ from the BMI SDS six months prior to the intervention (P = 0.46). One participant had a BMI SDS of 1.98 at recruitment three months prior to the intervention, but experienced weight loss resulting in a BMI SDS of 1.58 at start intervention, possibly due to linear growth following recent initiation of GH treatment. After 9 months, BMI SDS was significantly lower compared to baseline (median BMI SDS 2.47 vs BMI SDS 2.63, P = 0.04), with five of six participants showing a reduction in BMI SDS. At 12 months, overall BMI SDS was similar compared to baseline, although two participants demonstrated reduced BMI SDS (-0.19 and -0.14 SDS, respectively).

Figure 1. Change in BMI SDS from baseline

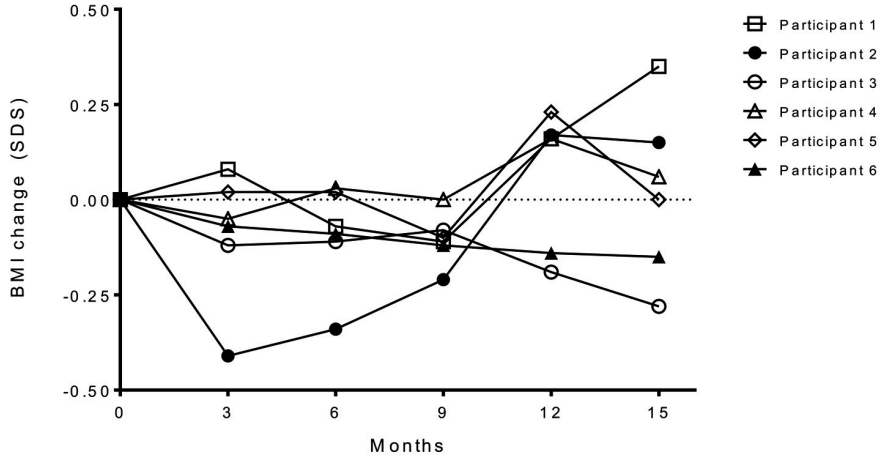


Table 2. Anthropomorphic measurements before, at 9 and 12 months of dietary intervention

	BMI (SDS)					Fat mass (kg)			Fat mass (%)			Waist circumference (cm)			Hip circumference (cm)		
Participant	Baseline	9-month	*P*	End of study	*P*	Baseline	End of study	*P*	Baseline	End of study	*P*	Baseline	End of study	*P*	Baseline	End of study	*P*
1.	3.07	2.96		3.23		44.6	49.5		42.9	45.8		102.0	103.0		114.5	120.0	
2.	2.18	1.97		2.35		24.2	29.1		38.9	42.4		82.4	86.0		89.0	96.0	
3.	1.91	1.83		1.72		25.3	24.9		35.2	34.1		90.0	87.0		90.0	90.0	
4.	5.10	5.10		5.26		86.5	95.7		51.5	51.5		133.0	160.0		160.0	160.0	
5.	1.58	1.48		1.81		20.0	24.2		38.3	41.6		84.0	85.0		79.2	84.0	
6.	4.44	4.32		4.30		53.7	55.2		50.9	53.5		115.0	118.0		110.0	119.0	
Median (range)	2.63 (1.58-5.10)	2.47 (1.48-5.10)	0.043	2.79 (1.72-5.26)	0.34	35.0 (20.0-86.5)	39.3 (24.2-95.7)	0.046	40.9 (35.2-51.5)	44.1 (34.1-53.5)	0.08	96.0 (82.4-133.0)	95.0 (85.0-160.0)	0.14	100.0 (79.2-160.0)	107.5 (84.0-160.0)	0.07

Energy intake

On the 5-day food record, participants reported similar daily energy intake after the 1-year intervention, compared to baseline (median 1638 kcal vs 1650 kcal, $P = 0.92$, Table 3). At baseline, two participants already reported to consume less calories, than the daily advised energy intake by the dietician. At the end of the intervention, two participants reported less calories than the dietician's advice (range -125 to -400 kcal), and four participants reported more calories than advised (range +475 to +525 kcal). One of the two participants who reported less caloric intake than advised, experienced a reduction in BMI SDS throughout the study (participant 6). In the total group, 60.3% of the total energy intake consisted of healthy products (i.e. green dots) at baseline, compared to 52.8% at the 12-month follow-up visit. Fluid intake greatly differed among study participants, as did the percentage of sugary beverages consumed (between 0 to 64.9% of total fluid intake at baseline). None of the participants' diets included the amounts and types of dietary components as recommended by the Dutch dietary guidelines (Table 3).

Metabolic outcomes

Overall, absolute fat mass increased between baseline and the 12-month follow-up (35.0 kg vs 39.3 kg, $P = 0.046$), although the percentage body fat remained stable (Table 2). No differences were observed for waist or hip circumferences between baseline and last follow-up, and none of the participants had hypertension at both time points. Participant 1 had elevated low-density lipoprotein and total cholesterol levels at baseline and at the 12-month follow-up visit. All participants had normal OGTT results at the baseline visit, but two participants demonstrated impaired glucose tolerance (*i.e.* glucose ≥ 7.8 mmol/L two hours post-OGTT) at the 12-month follow-up visit.

Physical activity

Compared to baseline, participants reported to be less inactive at the 12-month follow-up visit (207.3 min/day vs 47.3 min/day, $P = 0.028$), but no differences were observed for other activity levels (i.e. some inactivity, some activity, very active).

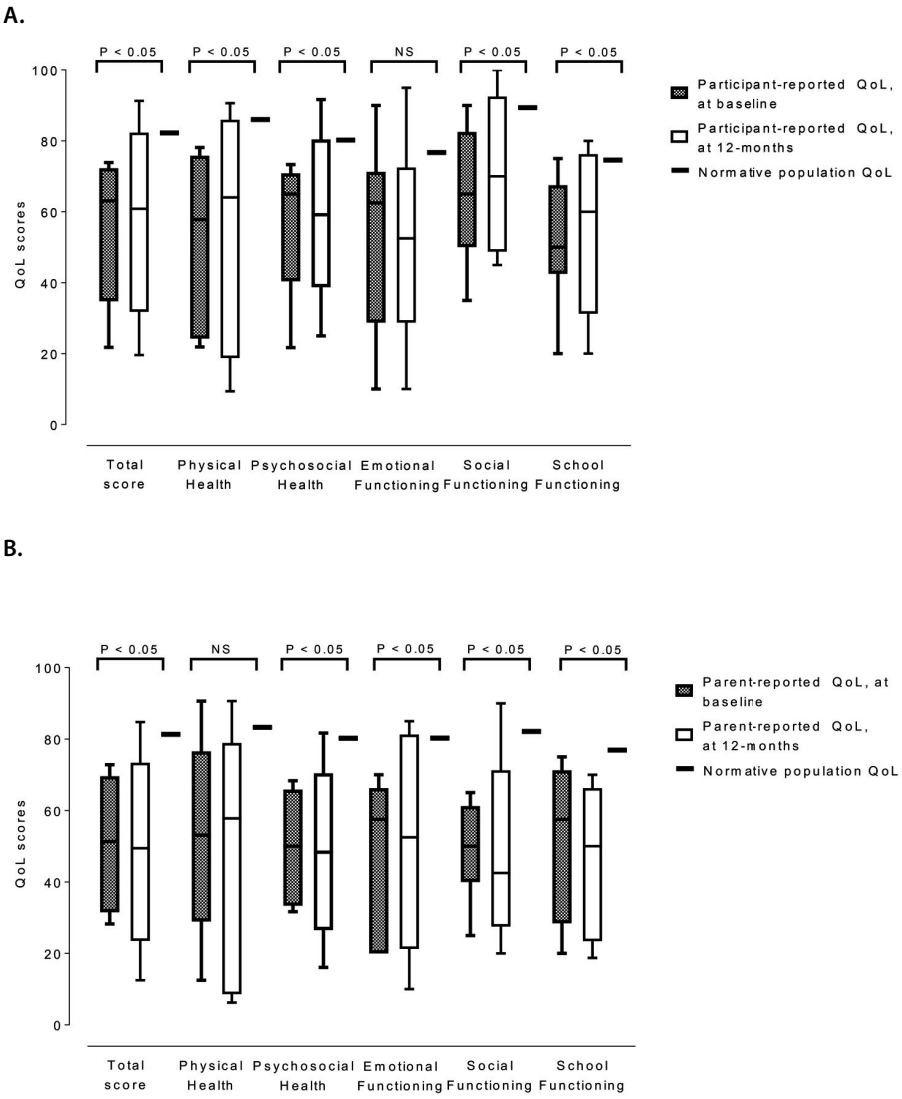
Quality of life

No significant differences in participant reported or parent proxy-reported total QoL or QoL subscales scores were observed after 1-year of intervention, compared to baseline. Participants tended to report their QoL higher, compared to parents, especially for social functioning (Figures 2A and 2B). When compared to normative values for children of the general Dutch population, participants reported significantly lower scores on total PedsQL (mean 55.43 ± 20.90 vs 82.24 ± 9.15, $P = 0.03$), and on all subscales, except for emotional functioning at start of the intervention (Figure 2A). Parents reported the perception of their child's total QoL lower (mean 50.80 ± 20.76 vs 81.34 ± 15.92, $P = 0.015$) as well as QoL of all subscales, compared to parents of children from the general population, except for physical health. (Figure 2B).

Table 3. Participant-reported energy intake before and after 12 months of dietary intervention

	Dietary advice (kcal)		Energy intake (kcal)						Fluid intake (mL)				Remarks by dietician	
Participant	Baseline	End of study	Baseline			End of study			Baseline		End of study		Baseline	End of study
			Total	Healthy choices	Less healthy choices	Total	Healthy choices	Less healthy choices	Total	Sugar	Total	Sugar		
1.	1425	1325	1781	903 (50.7%)	878 (49.3%)	1200	800 (66.7%)	400 (33.3%)	1600	500 (31.3%)	400	200 (50%)	Frequent use of unhealthy snacks Lack of bread and butter products	Underreporting suspected Lack of fruits and dairy products Unhealthy choices
2.	1225	1000	1795	1147 (63.9%)	648 (63.1%)	1525	825 (54.1%)	700 (45.9%)	1125	150 (13.3%)	488	0 (0%)	Lack of dairy products Unhealthy choices	Lack of dairy products Unhealthy choices
3.	1350	1350	1675	950 (56.7%)	725 (43.3%)	1825	925 (50.7%)	900 (49.3%)	925	600 (64.9%)	945	600 (63.5%)	Lack of fruits and dairy products	Lack of fruits and dairy products
4.	1275	1275	1215	942 (77.5%)	273 (22.5%)	1750	1000 (57.1%)	750 (42.9%)	Could not be determined	Could not be determined	Could not be determined	Could not be determined	Lack of dairy products	Lack of dairy products
5.	1425	1425	1625	725 (44.6%)	900 (55.4%)	1915	920 (48.0%)	995 (52.0%)	1050	150 (14.3%)	1100	450 (40.9%)	Lack of fruits, vegetables and butter products	Lack of fruits, vegetables and butter products
6.	1225	1225	950	675 (71.1%)	275 (28.9%)	825	425 (51.5%)	400 (48.5%)	1080	0 (0%)	920	0 (0%)	Lack of dairy products, fruits, vegetables, potatoes and meat	Lack of dairy products, fruits, vegetables, potatoes and meat

Figure 2. Participant (A) and parent-proxy (B) reports of Quality of life before and after 12 months of dietary intervention



Abbreviations: NS, not significant; QoL, quality of life

Evaluation of the intervention

Participants experienced more insight in their daily energy requirements and gain of nutrition knowledge (n=2). Also, increased satiety after food intake (n=2), successful weight loss (n=1) and individualized support from the coach were experienced as positive (n=3). Participants found it difficult to report their daily energy intakes (n=3). Suggestions for improvement included more support and involvement of the coach (n=3). Five participants would recommend this intervention to peers.

Parents experienced gain of nutrition knowledge (n=3), but also greater participants' responsibility for their own dietary choices (n=2). Parents reported difficulties with adherence to the intervention; the daily self-report of dietary intake was time- and energy consuming (n=4). Other difficulties included participants' increased drive to eat (n=2), decreased motivation during the study (n=2) and impaired visual or neurocognitive functioning of the child (n=2). Suggestions for improvement of the intervention included more involvement of the coach (n=2), more emphasis on healthy food consumption instead of caloric intake (n=1) and to create a user-friendly mobile application of the online platform (n=1). Five parents would recommend this intervention to others.

Discussion

As acquired HO following suprasellar tumors greatly impairs quality of life, there is an urgent need for new antiobesity interventions and specific treatment algorithms.[12] Our 1-year prospective pilot study demonstrates that children with HO are willing to participate in a dietary intervention (100% recruitment feasibility). Long-term adherence to this dietary intervention was, however, poor, and participants experienced difficulties with reporting their daily energy intakes. Second, significant BMI SDS reductions were observed after 9 months for the total group, although only 2 of 6 participants maintained this reduction at 12 months. Despite this overall lack of effectiveness at 12 months, increased insight into individual energy requirements, gain of nutrition knowledge, and the extensive support from a coach were experienced as positive by both participants and parents. These data support the need for dietary education and coaching in children with HO, and provide novel strategies how long-term adherence and effectiveness may be improved in future intervention studies.

There are several explanations for the poor adherence to the dietary intervention in this specific patient population. First, cognitive abilities required for self-report of energy intake include good memory and attention.[25] In children with suprasellar tumors, previous exposure to cranial radiotherapy and neurosurgical procedures can severely affect neurocognitive functioning, and thus limit their ability to adequately report food intake.[26] In addition, visual impairment raises practical issues with filling in online forms. Second, other tumor- and treatment related sequelae,

such as behavioral problems and sleeping disorders, and fear of tumor recurrence, may result in high physical and emotional burden for the child and their parents. This may impact participants' and parents' ability to dedicate and commit to dietary plans. Third, our study did not include direct parental involvement. Engagement of parents and the social environment may improve adherence to dietary interventions.[27]

Although the starting point of pediatric antiobesity management includes dietary modification, prospective studies that target eating behavior in children with HO are lacking.[12] In literature, one boy with acquired HO demonstrated significant weight loss of 38 kg after a protein-sparing modified fast program, although long-term follow-up effects were not reported.[28] Several other studies reported non-significant effects on BMI after dietary and exercise counseling prior to the start of their pharmacotherapeutic interventions.[29-31] Our study demonstrated BMI SDS reductions after 9 months of dietary intervention, which returned to baseline values at completion of the intervention. The regression of BMI to baseline values after 1-year of intervention is consistent with weight patterns as reported by dietary interventions in the general population.[32] Importantly, fluctuations in BMI may also negatively impact health outcomes with respect to cardiovascular morbidity, although effects in children remain unclear.[33] At completion of our intervention, total fat mass (in kg) was increased compared to baseline, and two participants demonstrated impaired glucose tolerance. The development of these adverse metabolic outcomes likely reflects the severity of HO and high risk for the metabolic syndrome in these children, rather than being a consequence of BMI fluctuations during the study.

Disturbed eating behavior has been reported in patients with craniopharyngioma, although inconsistencies among studies exist. Müller et al., reported pathological eating behaviors in patients with craniopharyngioma, especially in those with the highest BMIs.[9] In contrary, other reports show less energy intake in patients with craniopharyngioma, compared to a control population.[16] Throughout our study, it was remarkable that participants reported in about 70% of all days less nutrient intake than was recommended in their individualized dietary plans. Additionally, before the start of the intervention, two participants reported already lower caloric intakes than would be recommended by the dietician. One possible explanation is that our participants may have already achieved a certain weight balance with lower energy intake that matched their energy need, as their overall BMIs six months prior to the study were similar to baseline. Another explanation is that reduced physical activity and resting energy expenditure, rather than increased energy intake, is suggested to be the major contributor to HO in these children.[11,16] It remains unclear if we have overestimated the individual energy need, and if the dietary advice should even be more restrictive to achieve BMI reduction in this population. However, as none of the participants' diets met the recommendations of our Dutch dietary guidelines, one should be careful with even more stringent dietary restrictions. Finally,

participants may have systematically underreported their caloric intakes, including any food stealing behaviors, a phenomenon that is observed in these patients.[10,34]

It is well-known that QoL in children treated for craniopharyngioma or other suprasellar tumors can be negatively affected by the presence of HO.[7,35] Our participants and parents scored lower on many QoL domains, compared to normative populations. During the dietary intervention, QoL scores were not affected by changes in BMI SDS. This is in line with previous studies, that could not demonstrate associations between loss in BMI SDS and improvement of QoL, except for social functioning.[36] In children treated for craniopharyngioma or other suprasellar tumors, QoL may also be influenced by other tumor- or HO-related comorbidities, such as visual, neurological and neuroendocrine dysfunction. A multidisciplinary approach to target all co-morbid conditions has the potential to improve QoL in these children.[36]

Despite poor adherence and unsuccessful long-term BMI SDS reduction, the majority of participants and parents would recommend this intervention to others. Increased knowledge about nutrition and individual energy requirements were experienced as positive. This was surprising, as participants were already six years from tumor diagnosis, and all had previously received frequent and repetitive counselling about healthy eating patterns at our endocrinology clinic. Visualization of food products in green and orange dots, and close involvement of a dietician, may achieve better knowledge compared to dietary counselling in the outpatient clinic. The high number of contacts and positive attitudes of parents and participants towards the coach, support the need for psychosocial support while dieting.

Based on the experiences and results from this study, we provide several suggestions for improvement of a dietary intervention, and future research on this topic in general. First, reducing the frequency for self-reported dietary intake, and improving user-friendliness of the online platform (e.g. mobile application development) might result in better adherence. Second, more intensive support and involvement of the coach might have the ability to improve dietary adherence. Third, direct parental and social involvement should be included in future studies, as parents have the ability to better control food intake and create a healthy environment for their child.[37] Finally, dietary interventions may be considered as a first step in antiobesity treatment. However, treatment for HO may require multiple interventions that target simultaneously other domains contributing to HO.[12]

In conclusion, individualized dietary intervention with extensive coaching improves insight into dietary requirements and is able to reduce BMI SDS in some children with acquired HO. To achieve long-term BMI SDS reduction, more extensive coaching with direct involvement of parents and the social environment is needed. Simultaneously targeting other domains that contribute to the development of HO[12], may eventually improve HO and HO-associated comorbidities.

References

1. Karavitaki N, Brufani C, Warner JT, et al. Craniopharyngiomas in children and adults: systematic analysis of 121 cases with long-term follow-up. *Clin Endocrinol (Oxf).* 2005;62(4):397-409.
2. Sterkenburg AS, Hoffmann A, Gebhardt U, Warmuth-Metz M, Daubenbuchel AM, Muller HL. Survival, hypothalamic obesity, and neuropsychological/psychosocial status after childhood-onset craniopharyngioma: newly reported long-term outcomes. *Neuro Oncol.* 2015;17(7):1029-1038.
3. Haliloglu B, Atay Z, Guran T, et al. Risk factors for mortality caused by hypothalamic obesity in children with hypothalamic tumours. *Pediatr Obes.* 2016;11(5):383-388.
4. Muller HL, Bruhnken G, Emser A, et al. Longitudinal study on quality of life in 102 survivors of childhood craniopharyngioma. *Childs Nerv Syst.* 2005;21(11):975-980.
5. Merchant TE, Kiehna EN, Sanford RA, et al. Craniopharyngioma: the St. Jude Children's Research Hospital experience 1984-2001. *Int J Radiat Oncol Biol Phys.* 2002;53(3):533-542.
6. Muller HL, Bueb K, Bartels U, et al. Obesity after childhood craniopharyngioma--German multicenter study on pre-operative risk factors and quality of life. *Klin Padiatr.* 2001;213(4):244-249.
7. Poretti A, Grotzer MA, Ribi K, Schonle E, Boltshauser E. Outcome of craniopharyngioma in children: long-term complications and quality of life. *Dev Med Child Neurol.* 2004;46(4):220-229.
8. King BM. The rise, fall, and resurrection of the ventromedial hypothalamus in the regulation of feeding behavior and body weight. *Physiol Behav.* 2006;87(2):221-244.
9. Hoffmann A, Postma FP, Sterkenburg AS, Gebhardt U, Muller HL. Eating behavior, weight problems and eating disorders in 101 long-term survivors of childhood-onset craniopharyngioma. *J Pediatr Endocrinol Metab.* 2015;28(1-2):35-43.
10. Skorzewska A, Lal S, Waserman J, Guyda H. Abnormal food-seeking behavior after surgery for craniopharyngioma. *Neuropsychobiology.* 1989;21(1):17-20.
11. Bomer I, Saure C, Caminiti C, et al. Comparison of energy expenditure, body composition, metabolic disorders, and energy intake between obese children with a history of craniopharyngioma and children with multifactorial obesity. *J Pediatr Endocrinol Metab.* 2015;28(11-12):1305-1312.
12. van Iersel L, Brokke KE, Adan RAH, Bulthuis LCM, van den Akker ELT, van Santen HM. Pathophysiology and Individualized Treatment for Hypothalamic Obesity Following Craniopharyngioma and Other Suprasellar Tumors: A Systematic Review. *Endocr Rev.* 2018.
13. Jacola LM, Conklin HM, Scoggins MA, et al. Investigating the Role of Hypothalamic Tumor Involvement in Sleep and Cognitive Outcomes Among Children Treated for Craniopharyngioma. *J Pediatr Psychol.* 2016;41(6):610-622.
14. Wang KW, Chau R, Fleming A, et al. The effectiveness of interventions to treat hypothalamic obesity in survivors of childhood brain tumours: a systematic review. *Obes Rev.* 2017;18(8):899-914.
15. Styne DM, Arslanian SA, Connor EL, et al. Pediatric Obesity-Assessment, Treatment, and Prevention: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2017;102(3):709-757.
16. Harz KJ, Muller HL, Waldeck E, Pudel V, Roth C. Obesity in patients with craniopharyngioma: assessment of food intake and movement counts indicating physical activity. *J Clin Endocrinol Metab.* 2003;88(11):5227-5231.
17. Verreussel MJT, Dieleman JP, Rasenberg S, Veen-Roelofs J, van Baak MA: Obesity Treatment in Children with Intellectual Impairment: Outcome of a Multidisciplinary Inpatient Program. Obesity & Weight Loss Therapy 6:328, 2016.
18. Sullivan PB. *Feeding and Nutrition in Children with Neurodevelopmental Disability. London: Mac Keith Press, 2009: 57-85.*

19. Schonbeck Y, Talma H, van Dommelen P, et al. Increase in prevalence of overweight in Dutch children and adolescents: a comparison of nationwide growth studies in 1980, 1997 and 2009. *PLoS One.* 2011;6(11):e27608.

20. Kromhout D, Spaaij CJ, de Goede J, Weggemans RM. The 2015 Dutch food-based dietary guidelines. *Eur J Clin Nutr.* 2016;70(8):869-878.

21. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. *Med Care.* 2001;39(8):800-812.

22. Hay JA, Cairney J. Development of the habitual activityestimation scale for clinical research: a systematic approach.Pediatr Exerc Sci 2006;18:193–202

23. Engelen V, Haentjens MM, Detmar SB, Koopman HM, Grootenhuis MA. Health related quality of life of Dutch children: psychometric properties of the PedsQL in the Netherlands. *BMC Pediatr.* 2009;9:68.

24. Varni JW, Burwinkle TM, Seid M, Skarr D. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. *Ambul Pediatr.* 2003;3(6):329-341.

25. Livingstone MB, Robson PJ. Measurement of dietary intake in children. *Proc Nutr Soc.* 2000;59(2):279-293.

26. Kiehna EN, Mulhern RK, Li C, Xiong X, Merchant TE. Changes in attentional performance of children and young adults with localized primary brain tumors after conformal radiation therapy. *J Clin Oncol.* 2006;24(33):5283-5290.

27. Raber M, Swartz MC, Santa Maria D, et al. Parental involvement in exercise and diet interventions for childhood cancer survivors: a systematic review. *Pediatr Res.* 2016;80(3):338-346.

28. Lee YJ, Backeljauw PF, Kelly PD, Verdi PD, Redmond GP. Successful weight loss with protein-sparing modified fast in a morbidly obese boy with panhypopituitarism, diabetes insipidus, and defective thirst regulation. *Clin Pediatr (Phila).* 1992;31(4):234-236.

29. Fernandes JK, Klein MJ, Ater JL, Kuttesch JF, Vassilopoulou-Sellin R. Triiodothyronine supplementation for hypothalamic obesity. *Metabolism.* 2002;51(11):1381-1383.

30. Hamilton JK, Conwell LS, Syme C, Ahmet A, Jeffery A, Daneman D. Hypothalamic Obesity following Craniopharyngioma Surgery: Results of a Pilot Trial of Combined Diazoxide and Metformin Therapy. *Int J Pediatr Endocrinol.* 2011;2011:417949.

31. Lustig RH, Rose SR, Burghen GA, et al. Hypothalamic obesity caused by cranial insult in children: altered glucose and insulin dynamics and reversal by a somatostatin agonist. *J Pediatr.* 1999;135(2 Pt 1):162-168.

32. Johnston BC, Kanters S, Bandayrel K, et al. Comparison of weight loss among named diet programs in overweight and obese adults: a meta-analysis. *JAMA.* 2014;312(9):923-933.

33. Lissner L, Odell PM, D'Agostino RB, et al. Variability of body weight and health outcomes in the Framingham population. *N Engl J Med.* 1991;324(26):1839-1844.

34. Wehling H, Lusher J. People with a body mass index 30 under-report their dietary intake: A systematic review. *J Health Psychol.* 2017:1359105317714318.

35. Muller HL, Faldum A, Etavard-Gorris N, et al. Functional capacity, obesity and hypothalamic involvement: cross-sectional study on 212 patients with childhood craniopharyngioma. *Klin Padiatr.* 2003;215(6):310-314.

36. Rakhshani N, Jeffery AS, Schulte F, Barrera M, Atenafu EG, Hamilton JK. Evaluation of a comprehensive care clinic model for children with brain tumor and risk for hypothalamic obesity. *Obesity (Silver Spring).* 2010;18(9):1768-1774.

37. Meijneke RW, Schouten-van Meeteren AY, de Boer NY, et al. Hypothalamic obesity after treatment for craniopharyngioma: the importance of the home environment. *J Pediatr Endocrinol Metab.* 2015;28(1-2):59-63.

5

Clinical consequences of hypothalamic–pituitary disorders after conformal radiation therapy for pediatric low-grade glioma or ependymoma

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Submitted

Abstract

Objective

To determine the prevalence of hypothalamic-pituitary (HP) disorders, and their impact on health outcomes in children and adolescents who received focal conformal radiation therapy (RT) for central nervous system tumors.

Design, Patients, Measurements

Cohort study including 355 patients (age ≤25 years at diagnosis) treated with high-dose (50.4–59.4 Gy) RT using photons for low-grade glioma or ependymoma. Patients (median age 6.4 years at RT) received systematic endocrine follow-up (median duration 10.1 years, range 0.1–19.6). Associations between HP disorders, risk factors, and adverse health outcomes were determined by multivariable analysis.

Results

Prevalence was 37.2% for growth hormone deficiency (GHD), 17.7% for gonadotropin deficiency (LH/FSHD), 14.9% for thyroid-stimulating hormone deficiency (TSHD), 10.3% for adrenocorticotropic hormone deficiency (ACTHD), and 12.6% for central precocious puberty (CPP). Tumor involvement and shorter follow-up were associated with GHD, LH/FSHD, TSHD, and ACTHD. GHD was associated with short stature (OR 2.77; 95% CI 1.34–5.70) and low bone mineral density (OR 3.47; 95% CI 1.16–10.40), TSHD with dyslipidemia (OR 5.54; 95% CI 1.66–18.52). Patients with LH/FSHD, TSHD, ACTHD, and CPP had lower intelligence quotient scores. GHD, LH/FSHD, ACTHD, and CPP were associated with poorer attention scores; GHD, LH/FSHD, and ACTHD with lower memory scores. Treatment of GHD was not associated with increased risk for tumor recurrence, secondary tumors, or mortality.

Conclusions

HP disorders occur frequently in patients receiving high-dose RT, and are related to physical and neurocognitive well-being. Future studies are needed to assess whether further optimization of endocrine management yields better health outcomes.

Introduction

Central nervous system (CNS) tumors are the main purveyors of hypothalamic–pituitary (HP) disorders in children and adolescents treated for cancer.[1] Radiation therapy (RT) and tumor growth involving the HP region are risk factors for HP disorders and require lifelong endocrine surveillance.[2,3] In the general population, adverse effects of HP disorders, such as poor growth, increased cardiovascular morbidity, metabolic disorders, bone mineral density (BMD) deficit, and impaired neurocognitive functioning, have been well studied.[4,5]

Retrospective studies have reported the prevalence and risk factor associations of HP disorders in patients with CNS tumors or those previously exposed to cranial RT.[1,3,6] However, large studies with systematic and comprehensive endocrine follow-up are scarce. Also, data on clinical consequences of HP disorders in childhood cancer survivors (CCS) are limited and usually mainly focus on growth hormone (GH) deficiency (GHD).[7-10] Finally, whether GH treatment contributes to the risk of tumor recurrence, secondary tumors, and mortality remains controversial.[10]

Herein, we (1) determine the prevalence, risk factors, and latency times of HP disorders in a large population of systematically followed children and adolescent patients diagnosed with a CNS tumor and exposed to RT; (2) assess consequences of HP disorders on physical and neurocognitive outcomes; and (3) describe associations between GH treatment variables and risk for tumor recurrence, occurrence of secondary tumors, and mortality.

Methods

Patients

Patients diagnosed with ependymoma or low-grade glioma (LGG) before age 25 years and treated with RT using photons at a single institution between 1996 and 2016 were identified (n=355).

Data Collection

Sociodemographic and treatment data for primary CNS tumor diagnosis, relapse, or secondary tumor for eligible patients were retrospectively abstracted from medical and RT records after institutional review board approval. The prescribed RT dose to the primary site was 50.4-54 Gy for LGG and 54–59.4 Gy for ependymoma. Craniospinal irradiation (36-41.4 Gy) was administered to 12 patients with metastatic disease. Earliest patients were treated by prospective therapeutic protocols that included evaluation of endocrine function, growth, and development. The same evaluations were used in more recent patients as a standard and for those not specifically enrolled or treated by prospective protocols. Patients received ongoing follow-up in a dedicated late-effects clinic and then enrolled in a survivorship study for long-term monitoring and periodic follow-up appointments.[11] Neurocognitive testing was performed before RT treatment (baseline),

at 6 months, and yearly post-RT for a total of 5 years in patients on (RT1) protocol and as indicated by clinical referral.

Hypothalamic–Pituitary Disorders

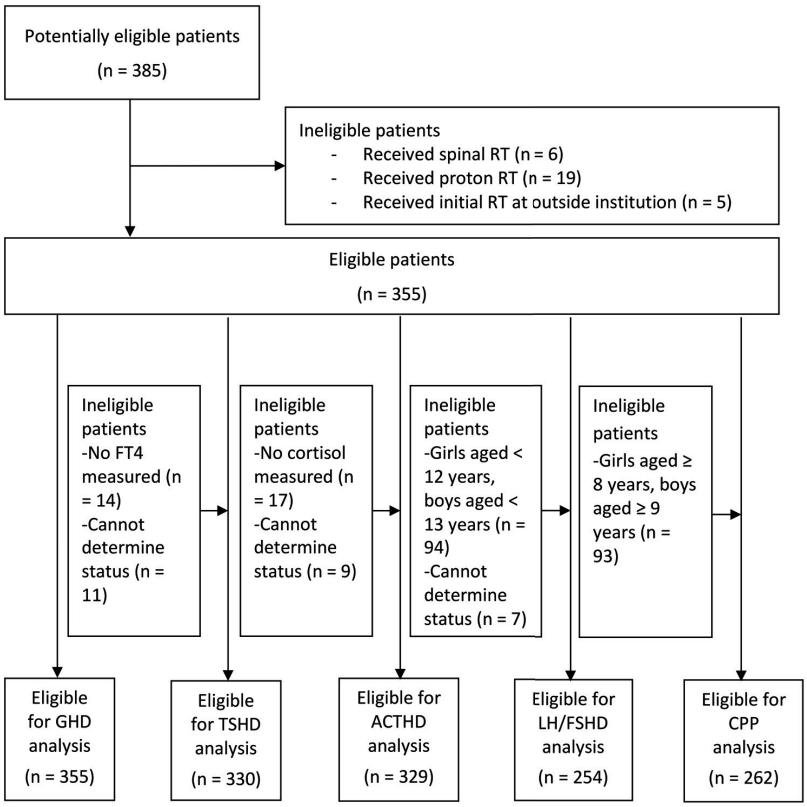
GHD was defined as GH peak response <10 ng/mL after provocative testing in children aged ≤16 years before January 2012 and as <5 ng/mL thereafter due to assay changes. For patients older than 16 years, a peak GH response <3 ng/mL was considered abnormal. Luteinizing hormone (LH)/follicle-stimulating hormone (FSH) deficiency (LH/FSHD) was diagnosed based on clinical examination (i.e. Tanner staging) in relation with chronological age, supplemented by laboratory values to prove the central origin of the deficit in sex hormones. Bone age delay was not used as a criterion for the diagnosis of LH/FSHD. In post-pubertal patients, LH/FSHD in males was defined by total testosterone <8.7 nmol/L (or 250 ng/dL), coinciding with LH <7 IU/L, and in females by secondary amenorrhea with estradiol <62 pmol/L (or 17 pg/mL) and FSH <11.2 IU/L. Thyroid-stimulating hormone (TSH) deficiency (TSHD) was diagnosed if free thyroxine concentrations were <12 pmol/L (or 0.9 ng/dL) and coincided with TSH <4 mIU/L. Adrenocorticotropic hormone deficiency (ACTHD) was based on abnormal results after dynamic testing; the low-dose ACTH test was most frequently used; a cortisol peak <500 nmol/L (or 18.1 µg/dL) 30 min after administering 1 µg ACTH intravenously was considered abnormal.[12] Central precocious puberty (CPP) was defined as onset of puberty based on Tanner 2 pubertal stage before age 8 and 9 years in girls and boys, respectively. Dates of onset of HP disorders and start/stop dates of hormonal replacement therapy, if applicable, were collected. Eligibility for analysis of specific HP disorders is outlined in Figure 1.

Physical Health Outcomes

Last-available measurements were used to characterize physical and neurocognitive health outcomes. Height and weight measurements were converted into age- and gender-adjusted z-scores for patients aged <20 years. Short stature was defined as a height z-score <–2 at last follow-up. Body mass index (BMI) was calculated as weight in kilograms (height in meters)^2 and converted into age- and gender-adjusted z-scores for patients aged <20 years. Obesity was defined as BMI z-score >2 for patients aged <20 years and absolute BMI ≥30 kg/m^2 in patients aged ≥20 years. Whole-body fat was calculated as total fat grams divided by total mass grams measured by whole-body dual-energy X-ray absorptiometry scans with a QDR 4500 fan-array scanner (Hologic) and expressed as percentage. Males and females with body fat ≥25% and ≥30%, respectively, were considered as having high fat mass. BMD was assessed by quantitative computed tomography (CT) with GE VCT Lightspeed 64-detector (GE Healthcare) and quantitative CT calibration phantoms and software (Mindways). Average volumetric trabecular BMD for lumbar vertebrae L1 and L2 was calculated and reported as age- and gender-adjusted

z-scores; low BMD was defined as a z-score <–2. Glucose disorder was considered present if patients had an elevated fasting insulin level (insulin ≥118 pmol/L or ≥17 mIU/L), impaired glucose tolerance (glucose ≥7.8 mmol/L or 140 mg/dL), overt diabetes mellitus type 2, and/or treatment with glucose-lowering medications. Patients with morning glucose ≥5.6 mmol/L (or 100 mg/dL) but <7.8 mmol/L were excluded from this analysis, as fasting state during blood withdrawal could not be determined for all patients. Fasting cholesterol, triglycerides, and high- and low-density lipoproteins (HDL and LDL) were measured by an enzymatic spectrophotometric assay (Modular P Chemistry Analyzer, Roche). Dyslipidemia was defined by either total cholesterol ≥5.2 mmol/L (or ≥200 mg/dL), LDL ≥3.4 mmol/L (or ≥130 mg/dL), HDL <1.0 mmol/L (or <40 mg/dL), triglycerides ≥1.7 mmol/L (or ≥150 mg/dL), and/or use of lipid-lowering medications. Patients on active therapy were excluded from this analysis because of potential treatment-induced dyslipidemia.

Figure 1. Flow diagram of the study cohort



Abbreviations: ACTHD, adrenocorticotropic hormone deficiency; CPP, central precocious puberty; FT4, free thyroxine; GHD, growth hormone deficiency; LH/FSHD, luteinizing hormone/follicle-stimulating hormone deficiency; RT, radiation therapy; TSHD, thyroid-stimulating hormone deficiency

Neurocognitive Outcomes

Intellectual ability was estimated by age-appropriate Wechsler scales. Due to high collinearity between Estimated Intellectual Quotient scores and Full Scale Intellectual Quotient scores, either score could be used to determine IQ.[13] Attention was assessed by Conners' Continuous Performance Test; the omission score was used as a measure of inattentiveness. Memory was assessed by total score from the age-appropriate version of the California Verbal Learning Test. Psychosocial functioning was assessed by parent report on the Child Behavior Checklist or Behavior Assessment System for Children, and internalizing index was used for analysis.

Statistical Analyses

Data were expressed as median (range). Descriptive analysis included (1) point prevalence: proportion of patients with each HP disorder, and (2) latency time: time between start of RT and onset of each HP disorder. As systematic screening for HP disorders was performed at start of RT and thereafter, HP disorders occurring before or within 6 months of the RT start date were excluded from latency time and risk factor analyses, as their onset may have preceded RT. Associations with gender, race, age at RT exposure, follow-up time, HP involvement of tumor, hydrocephalus with or without shunt, neurosurgery, alkylating agent, and relapse and/or secondary tumor were first tested in univariable models by chi-squared, exact chi-squared tests, and T-tests or nonparametric tests. Variables with $P \leq 0.1$ from univariable analyses were included in multivariable logistic regression models to determine independent associations with GHD, LH/FSHD, TSHD, and ACTHD post-RT exposure. Because CPP cases occurring after start of RT were limited, no multivariable risk factor analysis was performed for CPP. As patients eligible for outcomes LH/FSHD and CPP were limited, multivariable analysis for physical outcomes was adjusted only for either or all GHD, TSHD, and ACTHD, depending on their *P*-values in univariable analysis. Similarly, neurocognitive outcomes were adjusted only for patient and treatment characteristics possibly influencing neurocognitive functioning, but not for HP disorders. Univariable analysis for physical outcomes and multivariable analysis of the neurocognitive outcomes adjusted for HP disorders are given in Supplemental Tables 1 and 2, respectively. As a subset of GH-deficient patients never received GH replacement therapy, a subanalysis for the physical outcomes was performed only including GH-deficient individuals who received GH therapy during follow-up. Unadjusted logistic regression models were used for univariable analysis to assess associations between GH treatment variables and tumor recurrence, secondary tumors, and mortality. Patients (n=6) developing secondary tumors after a second RT course were excluded from this analysis. SAS version 9.4 (SAS Institute) was used for all analyses.

Results

Study Population

The study included 355 eligible patients (median age 17.8 years at last follow-up), with a median follow-up of 10.1 years (range, 0.1–19.6) from RT (Fig 1). Median age at RT exposure was 6.4 years (range, 0.9–24.9) and initial median RT dose was 54.0 Gy (range, 50.4–59.4). The cohort comprised 193 (54.4%) ependymoma and 162 (45.6%) LGG patients. Table 1 lists the cohort's baseline characteristics.

Table 1. Demographic and treatment characteristics of the study cohort

Variable	Patients, N=355	
	n	%
Gender		
Male	183	51.55
Female	172	48.45
Race		
White	275	77.46
Black	50	14.08
Other	30	8.45
Current status		
No evidence of disease	129	36.34
Stable disease	133	37.46
Progression of disease	13	3.66
Deceased	80	22.54
Age at tumor diagnosis (years)	Median	Range
	4.59	0.20–24.63
Age at follow-up (years)	Median	Range
	17.76	2.02–40.47
Follow-up duration from RT (years)	Median	Range
	10.09	0.12–19.59
Primary tumor diagnosis		
Ependymoma	193	54.37
Low-grade glioma	162	45.63
Primary location of tumor		
Supratentorial	45	12.68
Suprasellar	96	27.04
Infratentorial	213	60.00
Spinal cord	1	0.28

Table 1. Continued

Variable	Patients, N=355	
Hypothalamic–pituitary involvement		
Yes	103	29.01
No	252	70.99
Neurofibromatosis		
Yes	19	5.35
Neurofibromatosis, type 1	18	94.74
Neurofibromatosis, type 2	1	5.26
No	336	94.65
Hydrocephalus with or without shunt		
Yes	202	56.90
No	147	41.41
Unknown	6	1.69
Neurosurgery		
Yes	276	77.75
No	79	22.25
Chemotherapy		
Yes	125	35.21
No	229	64.51
Unknown	1	0.28
Alkylating agent		
Yes	58	16.34
No	292	82.25
Unknown	5	1.41
Age at start of RT (years)	Median	Range
	6.40	0.89–24.91
Primary RT location		
Cranial RT	343	96.61
Craniospinal RT	12	3.39
Primary RT dose (Gy)	Median	Range
	54.00	50.4-59.4
Tumor recurrence post-RT		
Yes	119	33.52
No	236	66.48
Second tumor		
Yes	28	7.89
No	327	92.11

Abbreviations: Gy, gray; RT, radiation therapy

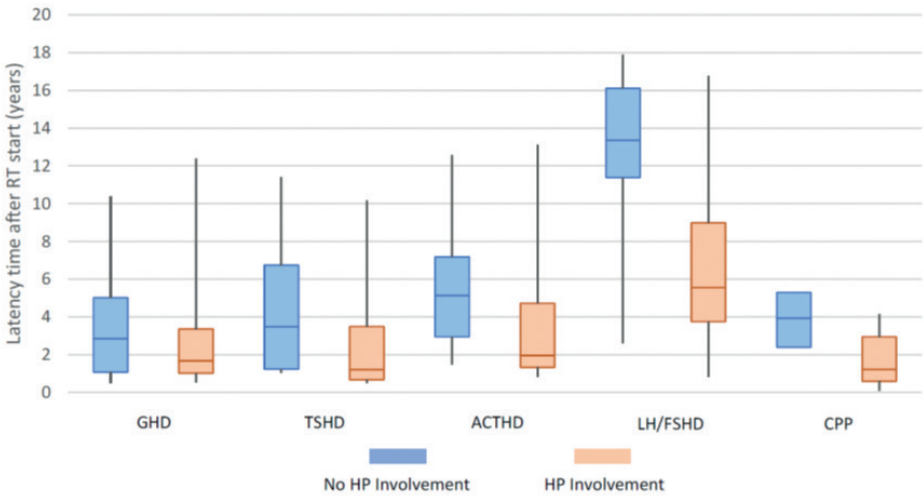
Prevalence and Risk Factors

In total, 132/355 patients (37.2%; 95% CI 32.1–42.4) had GHD, 45/254 eligible patients (17.7%; 95% CI 13.2–23.0) had LH/FSHD, 49/330 eligible patients (14.9%; 95% CI 11.2–19.2) had TSHD, 34/329 eligible patients (10.3%; 95% CI 7.3–14.1) had ACTHD, and 33/262 eligible patients (12.6%; 95% CI 8.8–17.2) had CPP (Supplemental Table 3). HP involvement and shorter follow-up time were independently associated with higher odds of GHD, LH/FSHD, TSHD, and ACTHD (Table 2). Younger age at RT exposure was significantly associated with GHD (OR 0.87; 95% 0.80–0.93). CPP prevalence was higher in patients with HP tumor involvement than patients without HP involvement (39.7% *v* 2.1%, respectively).

Latency Time

Of cases of HP disorders, 28/132 (21.2%) GHD, 2/45 (4.4%) LH/FSHD, 13/49 (26.5%) TSHD, 6/34 (17.6%) ACTHD, and 18/33 (54.5%) CPP occurred before or within 6 months after starting RT. Figure 2 illustrates latency times for HP disorders occurring after 6 months of RT completion. For TSHD (P=0.02), ACTHD (P=0.02) and LH/FSHD (P=0.002), latency times were significantly shorter in patients with HP tumor involvement, compared to patients without HP tumor involvement.

Figure 2. Latency times (median, interquartile range) after RT start for each hypothalamic–pituitary (HP) disorder, divided by either HP involvement or no HP involvement



Abbreviations: ACTHD, adrenocorticotropic hormone deficiency; CPP, central precocious puberty; GHD, growth hormone deficiency; HP, hypothalamic-pituitary; LH/FSHD, luteinizing hormone/follicle-stimulating hormone deficiency; RT, radiation therapy; TSHD, thyroid-stimulating hormone deficiency

Table 2. Multivariable analysis of risk factors associated with hypothalamic–pituitary disorders in the study cohort

Variable	GHD		TSHD		ACTHD		LH/FSHD	
	Yes N (row %)	OR (95% CI)	Yes N (row %)	OR (95% CI)	Yes N (row %)	OR (95% CI)	Yes N (row %)	OR (95% CI)
Gender								
Male	55 (32.35)	–	19 (11.73)	–	19 (11.45)	1.00	23 (19.01)	–
Female	49 (31.21)	–	17 (10.97)	–	9 (5.73)	0.48 (0.19–1.20)	20 (15.27)	–
Race								
White	87 (34.39)	1.00	27 (11.02)	–	21 (8.30)	–	32 (16.08)	–
Black	8 (17.78)	0.38 (0.14–1.03)	5 (11.11)	–	3 (6.67)	–	7 (20.00)	–
Other	9 (31.03)	0.48 (0.19–1.26)	4 (14.81)	–	4 (16.00)	–	4 (22.22)	–
Age at start of RT (years)	Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)	
Continuous	6.01 (4.12)	**0.87 (0.80–0.93)**	7.83 (5.62)	–	7.61 (5.88)	–	8.56 (4.33)	–
Follow-up time (years)	Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)	
Continuous	6.29 (5.06)	**0.72 (0.65–0.79)**	8.94 (5.49)	**0.72 (0.63–0.81)**	9.27 (5.35)	**0.79 (0.71–0.88)**	9.90 (5.90)	**0.90 (0.83–0.97)**
Hypothalamic–pituitary involvement								
No	61 (25.52)	1.00	14 (6.06)	1.00	11 (4.82)	1.00	10 (6.13)	1.00
Yes	43 (48.86)	**4.94 (2.41–10.09)**	22 (25.58)	**5.91 (2.13–16.38)**	17 (17.89)	**4.76 (2.00–11.36)**	33 (37.08)	**7.73 (3.20–18.71)**
Hydrocephalus with or without shunt								
No	36 (26.87)	1.00	10 (7.94)	–	11 (8.46)	–	14 (12.07)	1.00
Yes	67 (35.83)	1.04 (0.56–1.95)	25 (13.51)	–	17 (9.09)	–	28 (21.21)	1.78 (0.81–3.89)

Table 2. Continued

Variable	GHD		TSHD		ACTHD		LH/FSHD	
	Yes N (row %)	OR (95% CI)	Yes N (row %)	OR (95% CI)	Yes N (row %)	OR (95% CI)	Yes N (row %)	OR (95% CI)
Neurosurgery								
No	26 (37.14)	–	15 (22.73)	1.00	9 (12.68)	–	16 (27.12)	1.00
Yes	78 (30.35)	–	21 (8.37)	0.87 (0.30–2.53)	19 (7.54)	–	27 (13.99)	1.03 (0.44–2.43)
Relapse and/or second tumor								
No	66 (33.00)	–	16 (8.08)	1.00	17 (8.54)	–	24 (13.95)	1.00
Yes	38 (29.92)	–	20 (16.81)	1.44 (0.61–3.43)	11 (8.87)	–	19 (23.75)	1.30 (0.59–2.88)

Abbreviations: ACTHD, adrenocorticotropic hormone deficiency; CI, confidence interval; GHD, growth hormone deficiency; LH/FSHD, luteinizing hormone/follicle-stimulating hormone deficiency; OR, odds ratio; RT, radiation

Physical Outcomes and Hypothalamic-Pituitary Disorders

Of 132 patients with GHD, 84 (63.6%) were currently or previously receiving GH replacement therapy. Five patients received GH therapy before starting RT; remaining patients started GH therapy at a median of 3.28 years (range 0.94–12.28) post-RT completion. Of 33 patients with CPP, 30 (90.9%) received gonadotropin-releasing hormone analogues. LH/FSHD was treated with estrogen or testosterone in 35/45 (77.8%) patients. All patients with TSHD and ACTHD were on replacement therapy. Multivariable analysis revealed independent associations between GHD and short stature (OR 2.77; 95% CI 1.34–5.70) and low BMD (OR 3.47; 95% CI 1.16–10.40; Table 3). After excluding patients not given GH treatment from analysis, GHD was still associated with short stature (OR 2.44; 95% CI 1.01–5.90) but not low BMD (OR 2.98; 95% CI 0.84–10.57). Presence of TSHD was associated with higher odds of dyslipidemia (OR 5.54; 95% CI 1.66–18.52).

Neurocognitive Outcomes and Hypothalamic-Pituitary Disorders

Neurocognitive assessments were available for 263 (74.1%), 161 (45.4%), 211 (59.4%), and 206 (58.0%) patients for the intelligence, attention, memory, and psychosocial functioning domains, respectively. Median number of cognitive evaluations was 7 (range 1–12) for intelligence, 5 (range 1–17) for attention, 4 (range 1–10) for memory, and 5 (range 1–11) for psychosocial functioning. Our cohort had a higher proportion of below average performers (difference of 1SD) for all outcomes in comparison to the normative population (16%), except for psychosocial functioning. IQ scores were significantly lower in patients with LH/FSHD (82.8 *v* 96.6, *P*=0.01), TSHD (85.7 *v* 95.5, *P*=0.02), ACTHD (78.2 *v* 96.1, *P*=0.0002), and CPP (77.4 *v* 94.4, *P*=0.002) than those without these HP disorders (Table 3). Patients with GHD (*P*=0.02), LH/FSHD (*P*=0.01), ACTHD (*P*=0.01), and CPP (*P*=0.04) had poorer attention scores than patients without these HP disorders. GHD, LH/FSHD, and ACTHD were significantly associated with worse memory scores (*P*=0.0003, *P*=0.02, and *P*=0.02, respectively). No significant associations were found between psychosocial functioning and HP disorders.

Table 3. Multivariable analysis of physical and neurocognitive health outcomes associated with hypothalamic–pituitary disorders in the study cohort

	GHD				TSHD				ACTHD			
Physical outcomes†	**Yes N (row %)**	**No N (row %)**	**OR* (95% CI)**	**P-value**	**Yes N (row %)**	**No N (row %)**	**OR (95% CI)**	**P-value**	**Yes N (row %)**	**No N (row %)**	**OR (95% CI)**	**P-value**
Short stature	25 (20.16)	15 (7.81)	**2.77 (1.34–5.70)**	**0.01**	10 (20.41)	30 (11.24)	1.33 (0.57–3.09)	0.51	Not included in model			
Obesity	36 (29.03)	40 (20.83)	1.08 (0.60–1.93)	0.80	20 (40.82)	56 (20.97)	1.41 (0.61–3.27)	0.43	16 (47.06)	60 (21.28)	2.17 (0.88–5.37)	0.09
High fat mass	Not included in model				20 (95.24)	60 (75.00)	3.81 (0.45–32.36)	0.22	Not included in model			
Low BMD	21 (29.17)	5 (8.20)	**3.47 (1.16–10.40)**	**0.03**	10 (41.67)	16 (14.68)	1.72 (0.48–6.17)	0.40	8 (47.06)	18 (15.52)	2.53 (0.64-10.06)	0.19
Glucose disorder	Not included in model				15 (39.47)	56 (24.45)	1.18 (0.41–3.42)	0.77	10 (38.46)	61 (25.31)	0.98 (0.27-3.53)	0.98
Dyslipidemia	44 (57.14)	33 (36.26)	1.56 (0.74–3.27)	0.24	24 (77.42)	53 (38.69)	**5.54 (1.66–18.52)**	**0.01**	16 (69.57)	61 (42.07)	0.53 (0.13-2.15)	0.37

Table 3. Continued

	GHD			TSHD			ACTHD			LH/FSHD			CPP		
Neurocognitive outcomes‡	**Yes, adjust mean (SE)**	**No, adjust mean (SE)**	**P-value**	**Yes, adjust mean (SE)**	**No, adjust mean (SE)**	**P-value**	**Yes, adjust mean (SE)**	**No, adjust mean (SE)**	**P-value**	**Yes, adjust mean (SE)**	**No, adjust mean (SE)**	**P-value**	**Yes, adjust mean (SE)**	**No, adjust mean (SE)**	**P-value**
Intelligence	92.55 (2.13)	95.44 (1.79)	0.31	85.66 (3.83)	95.46 (1.42)	**0.02**	78.16 (4.55)	96.13 (1.39)	**0.0002**	82.77 (4.86)	96.57 (1.60)	**0.01**	77.38 (4.77)	94.38 (1.63)	**0.002**
Attention	83.05 (2.43)	75.27 (2.34)	**0.02**	87.08 (5.01)	77.30 (1.88)	0.07	92.04 (5.52)	77.05 (1.81)	**0.01**	92.93 (6.00)	76.90 (1.95)	**0.01**	95.13 (8.70)	75.91 (2.32)	**0.04**
Memory	34.46 (1.63)	42.66 (1.43)	**0.0003**	34.42 (2.91)	39.48 (1.21)	0.11	31.27 (3.41)	40.09 (1.19)	**0.02**	30.66 (3.46)	39.55 (1.30)	**0.02**	37.04 (4.06)	40.78 (1.30)	0.40
Psychosocial functioning	52.44 (1.49)	49.21 (1.14)	0.09	52.33 (2.74)	49.69 (0.99)	0.37	53.43 (3.17)	49.47 (0.94)	0.23	50.14 (3.66)	49.83 (1.06)	0.93	53.99 (3.22)	48.78 (1.04)	0.14

†Physical outcomes: All outcomes were adjusted for either GHD, TSHD and/or ACTHD, if P-value was ≤0.1 in univariable analysis. In addition, obesity and high fat mass were adjusted for hypothalamic-pituitary involvement. Glucose disorder and dyslipidemia were adjusted for obesity and age at last follow-up
‡Neurocognitive outcomes: All four neurocognitive outcomes were adjusted for age at start radiation therapy, neurofibromatosis, hydrocephalus with or without shunt and neurosurgery

Intellectual ability was estimated by age-appropriate Wechsler scales (Standard scores with mean of 100 and SD of 15). Attention was assessed by Conners' Continuous Performance Test; the omission score was used as a measure of inattentiveness (Percentiles with mean of 50 and SD of 34). Memory was assessed by total score from the age-appropriate version of the California Verbal Learning Test (T-scores with a mean of 50 and SD of 10). Psychosocial functioning was assessed by parent report on the Child Behavior Checklist or Behavior Assessment System for Children and, internalizing index was used for analysis (T-scores with a mean of 50 and SD of 10). A higher score indicates better performance on measures of intellectual ability and memory, but greater attention problems and parental concerns for measures of psychosocial functioning.

Abbreviations: ACTHD, adrenocorticotropic hormone deficiency; CI, confidence interval; GHD, growth hormone deficiency; LH/FSHD, luteinizing hormone/follicle-stimulating hormone deficiency; OR, odds ratio; RT, radiation therapy; SD, standard deviation; TSHD, thyroid-stimulating hormone deficiency *Empty cells represent variables that had a P-value >0.1 in univariable analysis and were thus not included for multivariable analysis.

Safety of Growth Hormone

Disease relapsed or progressed post-RT in 119 (33.5%). Occurrence of secondary tumors (*n*=28; 7.9%) was similar in patients receiving or not receiving GH therapy (OR 1.62; 95% CI 0.70–3.72). Supplemental Table 4 shows types of secondary tumors. Patients receiving GH therapy were less likely to experience relapse (OR 0.37; 95% CI 0.19–0.70) or death (OR 0.37; 95% CI 0.18–0.75). Duration of GH therapy was not associated with tumor relapse, secondary tumors or mortality.

Table 4. Unadjusted odds ratios for tumor recurrence, secondary tumor, and mortality

Variable	Tumor Recurrence		Secondary Tumor*		Mortality	
	Yes N (row %)	OR (95% CI)	Yes N (row %)	OR (95% CI)	Yes N (row %)	OR (95% CI)
GH treatment						
No	106 (89.08)	1.00	19 (7.09)	1.00	70 (26.12)	1.00
Yes	13 (10.92)	**0.37 (0.19–0.70)**	9 (10.98)	1.62 (0.70–3.72)	10 (11.49)	**0.37 (0.18–0.75)**
Duration GH treatment (years)†	Mean (SD)		Mean (SD)		Mean (SD)	
Continuous	9.36 (4.58)	0.93 (0.79–1.10)	8.79 (4.72)	1.13 (0.94–1.37)	8.58 (4.70)	0.86 (0.72–1.02)

*Patients with neurofibromatosis who developed benign peripheral nerve sheath tumors, were not considered as having a secondary tumor

†Patients with intermittent use of GH treatment were excluded for this analysis

Abbreviations: CI, confidence interval; GH, growth hormone; OR, odds ratio; RT, radiation therapy; SD, standard deviation

Discussion

This comprehensive and systematic study on a pediatric cohort with CNS tumors treated with RT reports prevalence, latency time, and risk factors for HP disorders with more certainty than previous studies. This study is especially unique due to the fact that we were able to asses associations between HP disorders and several adverse health outcomes. Novel findings include significant associations of HP disorders with impaired physical and neurocognitive health, despite early and frequent endocrine assessments. We also extend previous knowledge about the safety of GH treatment and risk for tumor recurrence, secondary tumors, and mortality.

A high proportion of patients experienced HP disorders, comparable to previous cohorts, although variations may exist by differences in follow-up time, screening protocols, and tumor or treatment characteristics.[1,3,13,14] Occurrence of HP disorders before start of RT is probably the consequence of tumor involvement in the HP region, a well-known risk factor for HP disorders, especially CPP.[15,16] HP involvement was also significantly associated with HP disorders developing post-RT; thus, tumor location remains an important risk factor during follow-up. HP disorders

seemed less likely to be newly diagnosed as time passed, especially in patients with HP tumor involvement, which underscores the usual trend of early occurrence in our homogenous and intensely treated cohort. High upper limits of latency times demonstrate, however, that HP disorders may still occur after longer follow-up, supporting previously reported time- and dose-dependent associations between HP disorders and RT.[17,18] Thus, despite the general trend of early occurrence of HP disorders post-RT, at-risk individuals require extended endocrine screening.[3]

Children treated for CNS tumors have impaired physical health, although how HP disorders affect adverse health outcomes is largely unknown. Timely replacement therapy for GHD may increase final height in CCS, although target heights cannot always be achieved.[19] In our patients, GHD was associated with short stature, even after excluding non–GH-treated patients, possibly due to delayed GH treatment and interruptions or complete cessation of treatment after relapse or secondary tumor. Children developing GHD and LH/FSHD post-RT have lower BMD scores.[20] In our cohort, GHD was associated with impaired BMD, although this association became nonsignificant when only GH-treated patients were included in analyses. This suggests that GH treatment can improve bone health in GH-deficient patients.[20] LH/FSHD was not associated with low BMD in univariable analysis. However, relatively young age at follow-up may have resulted in the short presence of LH/FSHD in our cohort. Adverse effects may be seen with longer follow-up.[3] Finally, CCS can have adverse metabolic outcomes (eg, abnormal lipid profiles, obesity, and high fat mass), although this has been mainly studied in survivors of acute lymphoblastic leukemia.[21,22] Increased occurrence of dyslipidemia in patients with TSHD in our study supports that TSHD contributes to adverse metabolic profiles in survivors. Also, GH treatment may improve outcomes as shown in cohorts of adult survivors treated for childhood cancers.[8,23] Although the presence of HP disorders increased the risk for obesity, glucose disorder, and dyslipidemia in univariable analyses, many associations became nonsignificant after adjusting for HP tumor involvement, possibly because of the overriding effect of direct hypothalamic injury.[24-26]

Greatest risk for neurocognitive impairment among patients with CNS tumors relates to tumor mass effect (eg, tumor size, hydrocephalus), treatment (eg, cranial RT, neurosurgery), or complications (eg, hemorrhage, vascular injury).[27] Besides direct damaging effects of tumor and treatment exposures, other comorbidities (eg, endocrine disorders), can contribute to neurocognitive impairment.[28] In our study, lower performance on measures of intelligence, attention, and memory was associated with multiple HP disorders. However, we cannot draw conclusions about the causality of HP disorders on neurocognitive impairment. In the general population, GHD can impair neurocognitive functioning, especially memory, although benefits of GH treatment remain uncertain due to lack of large intervention studies with sufficient follow-up.[29,30] For other HP disorders, studies on neurocognitive performance are scarce and mainly focus on deficiencies due to primary endocrine organ dysfunction.[31,32] Associations between HP

disorders and neurocognitive outcomes in our cohort are concerning, but whether these are causal or reflect a larger extent of brain injury should be investigated in large, well-designed studies.

In our patients, GH treatment was not associated with higher risk of secondary tumors, in line with most [33,34], but not all [35], reports. Similarly, a recent meta-analysis found no significant difference in the risk of secondary neoplasms in CCS treated with or without GH, although additional confirmatory studies with long-term follow-up are warranted.[10] Associations between GH treatment and reduced risk of tumor recurrence or mortality suggest that patients with a better prognosis were offered GH treatment. Indication and timing of GH treatment should be carefully determined after discussion with the patient and treating oncologist.[2]

The current study has several limitations. Presence of low BMD was defined by z-scores of the lumbar vertebrae, the most frequently assessed site in our cohort. Evaluations of other sites may have been more accurate, especially in patients who received craniospinal RT. The study of the effects of GHD on health outcomes included individuals who were on active GH therapy when the outcomes were assessed, as well those previously or never treated with GH. This may have resulted in a heterogeneous cohort, which we attempted to address by performing a subanalysis for GH-deficient patients who received GH replacement. Neurocognitive assessments were mainly performed on patients participating in specific RT protocols. This may have resulted in data being available only from specific subgroups. Finally, we included adolescents up to the age of 25 years at diagnosis. Although only a minority of patients (n=30) were >15 years at RT, their older age and post-pubertal status may have limited the impact of GHD and influenced the decision to initiate replacement, and associations with health outcomes.

In conclusion, we demonstrate that in patients exposed to high-dose RT after CNS tumor diagnosis, HP disorders occur frequently after a short follow-up. As HP disorders are associated with impaired health outcomes, there is a need for timely hormone replacement therapy in these patients. Timing and initiation of GH therapy should be carefully determined by a multidisciplinary team. GH treatment should only be initiated after counseling the patient and parents on its benefits and possible disadvantages. Impaired neurocognitive functioning in patients with HP disorders requires validation in future studies.

References

1. Clement SC, Schouten-van Meeteren AY, Boot AM, et al. Prevalence and Risk Factors of Early Endocrine Disorders in Childhood Brain Tumor Survivors: A Nationwide, Multicenter Study. *J Clin Oncol.* 2016;34(36):4362-4370.
2. Sklar CA, Antal Z, Chemaitilly W, et al. Hypothalamic-Pituitary and Growth Disorders in Survivors of Childhood Cancer: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2018;103(8):2761-2784.
3. Chemaitilly W, Li Z, Huang S, et al. Anterior hypopituitarism in adult survivors of childhood cancers treated with cranial radiotherapy: a report from the St Jude Lifetime Cohort study. *J Clin Oncol.* 2015;33(5):492-500.
4. Fleseriu M, Hashim IA, Karavitaki N, et al. Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2016;101(11):3888-3921.
5. Nieves-Martinez E, Sonntag WE, Wilson A, et al. Early-onset GH deficiency results in spatial memory impairment in mid-life and is prevented by GH supplementation. *J Endocrinol.* 2010;204(1):31-36.
6. Schmiegelow M, Lassen S, Poulsen HS, et al. Cranial radiotherapy of childhood brain tumours: growth hormone deficiency and its relation to the biological effective dose of irradiation in a large population based study. *Clin Endocrinol (Oxf).* 2000;53(2):191-197.
7. Link K, Moell C, Garwicz S, et al. Growth hormone deficiency predicts cardiovascular risk in young adults treated for acute lymphoblastic leukemia in childhood. *J Clin Endocrinol Metab.* 2004;89(10):5003-5012.
8. Follin C, Thilen U, Osterberg K, Bjork J, Erfurth EM. Cardiovascular risk, cardiac function, physical activity, and quality of life with and without long-term growth hormone therapy in adult survivors of childhood acute lymphoblastic leukemia. *J Clin Endocrinol Metab.* 2010;95(8):3726-3735.
9. van den Heijkant S, Hoorweg-Nijman G, Huisman J, et al. Effects of growth hormone therapy on bone mass, metabolic balance, and well-being in young adult survivors of childhood acute lymphoblastic leukemia. *J Pediatr Hematol Oncol.* 2011;33(6):e231-238.
10. Tamhane S, Sfeir JG, Kittah NEN, et al. GH Therapy in Childhood Cancer Survivors: A Systematic Review and Meta-Analysis. *J Clin Endocrinol Metab.* 2018;103(8):2794-2801.
11. Hudson MM, Ness KK, Nolan VG, et al. Prospective medical assessment of adults surviving childhood cancer: study design, cohort characteristics, and feasibility of the St. Jude Lifetime Cohort study. *Pediatr Blood Cancer.* 2011;56(5):825-836.
12. Charmandari E, Nicolaides NC, Chrousos GP. Adrenal insufficiency. *Lancet.* 2014;383(9935):2152-2167.
13. Armstrong GT, Conklin HM, Huang S, et al. Survival and long-term health and cognitive outcomes after low-grade glioma. *Neuro Oncol.* 2011;13(2):223-234.
14. Gan HW, Phipps K, Aquilina K, Gaze MN, Hayward R, Spoudeas HA. Neuroendocrine Morbidity After Pediatric Optic Gliomas: A Longitudinal Analysis of 166 Children Over 30 Years. *J Clin Endocrinol Metab.* 2015;100(10):3787-3799.
15. Karavitaki N, Brufani C, Warner JT, et al. Craniopharyngiomas in children and adults: systematic analysis of 121 cases with long-term follow-up. *Clin Endocrinol (Oxf).* 2005;62(4):397-409.
16. Chemaitilly W, Merchant TE, Li Z, et al. Central precocious puberty following the diagnosis and treatment of paediatric cancer and central nervous system tumours: presentation and long-term outcomes. *Clin Endocrinol (Oxf).* 2016;84(3):361-371.
17. Vatner RE, Niemierko A, Misra M, et al. Endocrine Deficiency As a Function of Radiation Dose to the Hypothalamus and Pituitary in Pediatric and Young Adult Patients With Brain Tumors. *J Clin Oncol.* 2018;36(28):2854-2862.

18. Merchant TE, Rose SR, Bosley C, Wu S, Xiong X, Lustig RH. Growth hormone secretion after conformal radiation therapy in pediatric patients with localized brain tumors. *J Clin Oncol.* 2011;29(36):4776-4780.

19. Gleeson HK, Stoeter R, Ogilvy-Stuart AL, Gattamaneni HR, Brennan BM, Shalet SM. Improvements in final height over 25 years in growth hormone (GH)-deficient childhood survivors of brain tumors receiving GH replacement. *J Clin Endocrinol Metab.* 2003;88(8):3682-3689.

20. Cohen LE, Gordon JH, Popovsky EY, et al. Bone density in post-pubertal adolescent survivors of childhood brain tumors. *Pediatr Blood Cancer.* 2012;58(6):959-963.

21. Green DM, Cox CL, Zhu L, et al. Risk factors for obesity in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *J Clin Oncol.* 2012;30(3):246-255.

22. Nottage KA, Ness KK, Li C, Srivastava D, Robison LL, Hudson MM. Metabolic syndrome and cardiovascular risk among long-term survivors of acute lymphoblastic leukaemia - From the St. Jude Lifetime Cohort. *Br J Haematol.* 2014;165(3):364-374.

23. Murray RD, Darzy KH, Gleeson HK, Shalet SM. GH-deficient survivors of childhood cancer: GH replacement during adult life. *J Clin Endocrinol Metab.* 2002;87(1):129-135.

24. Wijnen M, Olsson DS, van den Heuvel-Eibrink MM, et al. The metabolic syndrome and its components in 178 patients treated for craniopharyngioma after 16 years of follow-up. *Eur J Endocrinol.* 2018;178(1):11-22.

25. Holmer H, Pozarek G, Wirfalt E, et al. Reduced energy expenditure and impaired feeding-related signals but not high energy intake reinforces hypothalamic obesity in adults with childhood onset craniopharyngioma. *J Clin Endocrinol Metab.* 2010;95(12):5395-5402.

26. Roth CL, Gebhardt U, Muller HL. Appetite-regulating hormone changes in patients with craniopharyngioma. *Obesity (Silver Spring).* 2011;19(1):36-42.

27. Krull KR, Hardy KK, Kahalley LS, Schuitema I, Kesler SR. Neurocognitive Outcomes and Interventions in Long-Term Survivors of Childhood Cancer. *J Clin Oncol.* 2018;36(21):2181-2189.

28. Cheung YT, Brinkman TM, Li C, et al. Chronic Health Conditions and Neurocognitive Function in Aging Survivors of Childhood Cancer: A Report from the Childhood Cancer Survivor Study. *J Natl Cancer Inst.* 2018;110(4):411-419.

29. Nyberg F, Hallberg M. Growth hormone and cognitive function. *Nat Rev Endocrinol.* 2013;9(6):357-365.

30. Arwert LI, Deijen JB, Witlox J, Drent ML. The influence of growth hormone (GH) substitution on patient-reported outcomes and cognitive functions in GH-deficient patients: a meta-analysis. *Growth Horm IGF Res.* 2005;15(1):47-54.

31. Kempers MJ, van der Sluijs Veer L, Nijhuis-van der Sanden RW, et al. Neonatal screening for congenital hypothyroidism in the Netherlands: cognitive and motor outcome at 10 years of age. *J Clin Endocrinol Metab.* 2007;92(3):919-924.

32. Tiemensma J, Andela CD, Biermasz NR, Romijn JA, Pereira AM. Mild cognitive deficits in patients with primary adrenal insufficiency. *Psychoneuroendocrinology.* 2016;63:170-177.

33. Patterson BC, Chen Y, Sklar CA, et al. Growth hormone exposure as a risk factor for the development of subsequent neoplasms of the central nervous system: a report from the childhood cancer survivor study. *J Clin Endocrinol Metab.* 2014;99(6):2030-2037.

34. Mackenzie S, Craven T, Gattamaneni HR, Swindell R, Shalet SM, Brabant G. Long-term safety of growth hormone replacement after CNS irradiation. *J Clin Endocrinol Metab.* 2011;96(9):2756-2761.

35. Ergun-Longmire B, Mertens AC, Mitby P, et al. Growth hormone treatment and risk of second neoplasms in the childhood cancer survivor. *J Clin Endocrinol Metab.* 2006;91(9):3494-3498.

Supplementary material

Supplemental Table 1. Univariable analysis of physical health outcomes associated with hypothalamic-pituitary disorders in the study cohort

	GHD				TSHD				ACTHD				LH/FSHD				CPP			
Physical health outcomes	**Yes N (row %)**	**No N (row %)**	**OR (95% CI)**	**P-value**	**Yes N (row %)**	**No N (row %)**	**OR (95% CI)**	**P-value**	**Yes N (row %)**	**No N (row %)**	**OR (95% CI)**	**P-value**	**Yes N (row %)**	**No N (row %)**	**OR (95% CI)**	**P-value**	**Yes N (row %)**	**No N (row %)**	**OR (95% CI)**	**P-value**
Short stature	27 (20.45)	19 (8.52)	2.76 (1.47–5.20)	**0.002**	10 (20.41)	30 (10.68)	2.15 (0.97–4.73)	0.06	7 (20.59)	38 (12.88)	1.75 (0.71–4.31)	0.22	9 (20.00)	23 (11.00)	2.02 (0.87–4.73)	0.10	6 (18.18)	34 (14.85)	1.28 (0.49–3.32)	0.62
Obesity	38 (28.79)	43 (19.28)	1.69 (1.02–2.80)	**0.04**	20 (40.82)	59 (21.00)	2.60 (1.37–4.91)	**0.003**	16 (47.06)	61 (20.68)	3.41 (1.64–7.08)	**0.001**	20 (44.44)	40 (19.14)	3.38 (1.71–6.68)	**0.0005**	15 (45.45)	42 (18.34)	3.71 (1.73–7.95)	**0.0008**
High fat mass	53 (85.48)	33 (73.33)	2.14 (0.81–5.63)	0.12	21 (95.45)	64 (76.19)	6.56 (0.83–51.90)	0.07	14 (100)	67 (76.14)	–	–	22 (95.65)	60 (75.00)	7.33 (0.93–57.92)	0.06	10 (90.91)	42 (76.36)	3.09 (0.36–26.50)	0.30
Low BMD	23 (29.49)	6 (8.96)	4.25 (1.61–11.21)	**0.003**	11 (40.74)	18 (15.65)	3.71 (1.48–9.28)	**0.01**	8 (47.06)	20 (16.53)	4.49 (1.55–13.04)	**0.01**	7 (29.17)	18 (16.82)	2.04 (0.74–5.62)	0.17	5 (35.71)	18 (21.95)	1.98 (0.59–6.64)	0.27
Glucose disorder	32 (28.57)	43 (22.63)	1.37 (0.80–2.33)	0.25	20 (46.51)	61 (24.80)	2.64 (1.36–5.13)	**0.004**	14 (46.67)	65 (25.39)	2.57 (1.19–5.56)	**0.02**	15 (46.88)	53 (29.61)	2.10 (0.98–4.51)	**0.06**	20 (62.50)	37 (18.50)	7.34 (3.30–16.33)	**<0.0001**
Dyslipi-demia	44 (56.41)	38 (39.18)	2.01 (1.10–3.68)	**0.02**	24 (77.42)	58 (40.56)	5.03 (2.03–12.43)	**0.0005**	16 (69.57)	65 (43.33)	2.99 (1.16–7.69)	**0.02**	25 (75.76)	55 (41.35)	4.43 (1.86–10.55)	**0.0008**	18 (78.26)	39 (39.39)	5.54 (1.90–16.14)	**0.002**

*Abbreviations: ACTHD, adrenocorticotropic hormone deficiency; BMD, bone mineral density; CI, confidence interval; CPP, central precocious puberty; GHD, growth hormone deficiency; LH/FSHD, luteinizing hormone/follicle-stimulating hormone deficiencies; OR, odds ratio; thyroid-stimulating hormone deficiency.

Supplemental Table 2. Multivariable analysis, adjusted for hypothalamic-pituitary disorders, of neurocognitive outcomes associated with hypothalamic-pituitary disorders among the study cohort

	GHD			TSHD			ACTHD			LH/FSHD			CPP		
Neurocognitive outcomes*	**Yes, adjust mean (SE)**	**No, adjust mean (SE)**	**P-value**	**Yes, adjust mean (SE)**	**No, adjust mean (SE)**	**P-value**	**Yes, adjust mean (SE)**	**No, adjust mean (SE)**	**P-value**	**Yes, adjust mean (SE)**	**No, adjust mean (SE)**	**P-value**	**Yes, adjust mean (SE)**	**No, adjust mean (SE)**	**P-value**
Intelligence	91.40 (2.40)	90.95 (2.59)	0.90	101.84 (5.92)	88.75 (2.21)	0.07	68.05 (6.92)	94.56 (1.94)	**0.001**	87.11 (7.26)	92.00 (2.07)	0.56	77.04 (4.83)	94.60 (2.03)	**0.002**
Attention	83.62 (3.19)	74.82 (3.97)	0.08	86.66 (9.28)	77.91 (3.29)	0.43	82.41 (10.35)	79.13 (2.98)	0.78	83.65 (11.94)	78.74 (3.18)	0.72	86.85 (8.87)	77.79 (3.01)	0.37
Memory	34.90 (1.97)	41.46 (1.72)	**0.02**	Not included in model			36.74 (4.62)	39.04 (1.33)	0.64	34.99 (4.28)	39.36 (1.38)	0.36	Not included in model		
Psychosocial functioning	n.a.														

*All four neurocognitive outcomes were adjusted for age at start radiation therapy, neurofibromatosis, hydrocephalus with or without shunt, neurosurgery and for specific HP disorders, if P-value was ≤0.1 in univariable analysis. ǂ For psychosocial functioning, none of the P-values of HP disorders were ≤0.1 in univariable analysis.
Intellectual ability was estimated by age-appropriate Wechsler scales (Standard scores with mean of 100 and SD of 15). Attention was assessed by Conners' Continuous Performance Test; the omission score was used as a measure of inattentiveness (Percentiles with mean of 50 and SD of 34). Memory was assessed by total score from the age-appropriate version of the California Verbal Learning Test (T-scores with a mean of 50 and SD of 10). Psychosocial functioning was assessed by the Parent Rating Scale, and internalizing index was used for analysis (T-scores with a mean of 50 and SD of 10). A higher score indicates better performance on measures of intellectual ability and memory, but greater attention problems and parental concerns for measures of psychosocial functioning.
Abbreviations: ACTHD, adrenocorticotropic hormone deficiency; CPP, central precocious puberty; GHD, growth hormone deficiency; LH/FSHD, luteinizing hormone/follicle-stimulating hormone deficiencies; n.a.; not applicable; SE, standard error; TSHD, thyroid-stimulating hormone deficiency

Supplemental Table 3. Point prevalence of hypothalamic–pituitary disorders

	GHD	TSHD	ACTHD	LH/FSHD	CPP
All patients (n=355)	N=355	N=330	N=329	N=254	N=262
	37.18%	14.85%	10.33%	17.72%	12.60%
	95% CI 32.14–42.44	95% CI 11.19–19.15	95% CI 7.26–14.14	95% CI 13.23–22.98	95% CI 8.83–17.23
Patients without HP tumor involvement (n=252)	N=252	N=232	N=229	N=164	N=189
	29.37%	6.47%	5.24%	6.71%	2.12%
	95% CI 23.82–35.41	95% CI 3.66–10.44	95% CI 2.74–8.97	95% CI 3.40–11.68	95% CI 0.58–5.33
Patients with HP tumor involvement (n=103)	N=103	N=98	N=100	N=90	N=73
	56.31%	34.69%	22.00%	37.78%	39.73%
	95% CI 46.18–66.06	95% CI 25.36–44.98	95% CI 14.33–31.39	95% CI 27.77–48.62	95% CI 28.45–51.86

Abbreviations: ACTHD, adrenocorticotropic hormone deficiency; CI, confidence interval; CPP, central precocious puberty; GHD, growth hormone deficiency; HP, hypothalamic–pituitary; LH/FSHD, luteinizing hormone/follicle-stimulating hormone deficiency; TSHD, thyroid-stimulating hormone deficiency

Supplemental Table 4. Types of secondary tumors

Second tumor	GH treated (N, row %)	GH-untreated (N, row %)	Total (N, row %)
Meningioma	2 (22.22)	4 (21.05)	6 (21.43)
Glioma	1 (11.11)	4 (21.05)	5 (17.86)
Thyroid carcinoma	1 (11.11)	3 (15.79)	4 (14.29)
Glioblastoma	–	3 (15.79)	3 (10.71)
MPNST	2 (22.22)	1 (5.26)	3 (10.71)
Astrocytoma	1 (11.11)	1 (5.26)	2 (7.14)
Basal cell carcinoma, skull	1 (11.11)	–	1 (3.57)
Desmoid tumor	–	1 (5.26)	1 (3.57)
Ewing sarcoma	–	1 (5.26)	1 (3.57)
Non-melanoma skin cancer	1 (11.11)	–	1 (3.57)
Renal cell carcinoma	–	1 (5.26)	1 (3.57)

Abbreviations: MPNST, malignant peripheral nerve sheath tumor

6

Hypothalamic-pituitary disorders in survivors of childhood cancer: a report from the St. Jude Lifetime Cohort Study

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Submitted

Abstract

Context: Data on hypothalamic-pituitary (HP) disorders in systematically evaluated childhood cancer survivors are limited.

Objective: To describe prevalence, risk factors and associated adverse health outcomes of deficiencies in GH (GHD), TSH (TSHD), LH/FSH (LH/FSHD) and ACTH (ACTHD) as well as central precocious puberty (CPP).

Design: Retrospective with cross-sectional health outcomes analysis.

Setting: Established cohort; tertiary care center.

Patients: 3141 participants (median age, 31.7 years) followed for median 24.1 years.

Main outcome measure: Multivariable logistic regression was used to calculate odds ratios and 95% confidence intervals for associations between HP disorders, tumor / treatment-related risk factors and health outcomes.

Results: Among participants exposed to cranial radiotherapy (RT), the estimated prevalence was 40.2% for GHD, 11.1% for TSHD, 10.6% for LH/FSHD, 3.2% for ACTHD, and 0.9% for CPP. Participants not exposed to RT demonstrated a prevalence of 6.2% for GHD, and <1% for other HP disorders. Clinical factors independently associated with HP disorders included RT (at any dose for GHD, TSHD, LH/FSHD, > 30 Gy for ACTHD), alkylating agents (GHD, LH/FSHD), intrathecal chemotherapy (GHD), hydrocephalus with shunt placement (GHD, LH/FSHD), seizures (TSHD, ACTHD) and stroke (GHD, TSHD, LH/FSHD, ACTHD). Adverse health outcomes independently associated with HP disorders included short stature (GHD, TSHD), severe bone mineral density deficit (GHD, LH/FSHD), obesity (LH/FSHD), frailty (GHD), impaired physical health-related quality of life (TSHD), sexual dysfunction (LH/FSHD), and impaired memory and processing speed (GHD, TSHD).

Conclusions: Cranial radiotherapy, CNS injury and, to a lesser extent, chemotherapy are associated with HP disorders, which are associated with adverse health outcomes.

Introduction

Improvement in survival of children diagnosed with cancer and research demonstrating high rates of chronic disease and early mortality in adult survivors of childhood cancer highlight the importance of characterizing clinical factors contributing to those morbidities.[1] Hypothalamic-pituitary (HP) disorders are frequently observed sequelae in childhood cancer survivors [2-4], and when present are associated with impaired growth, pubertal development and reproductive function, suboptimal body composition, decreased bone mineral density (BMD), inability to respond to medical stress, and poor quality of life.[5,6]

Cranial radiation therapy (RT) and tumor location in the HP region are established risk factors for HP disorders.[7,8] The occurrence of HP disorders in survivors exposed to chemotherapy or in individuals with other health conditions associated with CNS injury, is not well documented.[9] In addition, data on the contribution of specific HP disorders to physical, psychosocial and neurocognitive health are limited.

A previous report from the St. Jude Lifetime Cohort (SJLIFE) described the prevalence of HP disorders among childhood cancer survivors treated with cranial RT.[10] SJLIFE expanded endocrine surveillance after 2015 from screening only at-risk participants (i.e. those exposed to RT), to screening all participants, regardless of previous treatment exposures. This change has provided a unique opportunity to characterize potential risk factors for HP disorders in individuals not exposed to cranial RT. Therefore, the aims of this study were to: 1) describe the prevalence of HP disorders in long-term clinically assessed childhood cancer survivors, including those not exposed to RT; 2) evaluate associations between sociodemographic and treatment-related risk factors and HP disorders; and, 3) describe associations between HP disorders and overall physical, psychosocial and neurocognitive well-being.

Methods

SJLIFE study

Participants were enrolled in the previously described Institutional Review Board–approved SJLIFE study.[11,12] SJLIFE is a retrospective cohort study initiated in April 2007 with prospective periodic follow-up and ongoing clinical data collection designed to facilitate clinical assessment of late health outcomes of long-term childhood cancer survivors.

Eligibility

Survivors diagnosed with cancer ≤18 years of age, treated for childhood cancer at St. Jude Children's Research Hospital and who were at least five years from cancer diagnosis, were considered eligible for the current analysis. Participants underwent a comprehensive clinical

assessment between 2007 and 2016 on the St. Jude campus including measures of physical, psychosocial and neurocognitive health.

Tumor and Treatment variables

Central nervous system (CNS) tumors were classified as involving the HP region if they included the thalamus, hypothalamus, optic chiasm, third ventricle and sellar or parasellar region. Dosimetry, allowing HP dose calculations, was available for 921 of 1086 cranially irradiated participants. The RT dose absorbed by the HP region was based on prescribed doses for direct exposures. For indirect exposures, HP doses were estimated using radiation oncology records as previously described.[13] In the remaining 165 participants exposed to cranial RT, the RT dose was quantified by the maximum tumor prescribed dose to the brain. Stroke was defined as any Common Terminology Criteria for Adverse Events (CTCAE) grade 2 or higher cerebrovascular accident, cerebrovascular disease or intracranial hemorrhage. Survivors with previous placement of ventriculoperitoneal or ventriculoatrial shunts were classified with a history of hydrocephalus.

Diagnoses of HP disorders

In participants receiving hormone replacement therapy at the time of their visit, HP disorders were validated by medical record review. In those not receiving hormone replacement therapy, HP disorders were determined from values in a morning blood sample at the SJLIFE visit, described previously.[10] Briefly, GHD was considered present if age and sex specific insulin-like growth factor 1 (IGF-1) was <-2SD. Participants without available IGF-1 measurements or those with liver fibrosis and/or liver cirrhosis, conditions known to reduce synthesis of IGF-1, were excluded from GHD analysis. TSH deficiency (TSHD) was defined if free thyroxine was <0.9 ng/dL and TSH <4 mIU/L. LH/FSH deficiency (LH/FSHD) in males was defined by total testosterone less than 200 ng/dL before March 1, 2012 and 250 ng/dL afterwards (due to changes in assays used), in the presence of an LH less than 7 IU/L and FSH less than 9.2 IU/L. In females, LH/FSHD was defined if primary or secondary amenorrhea occurred before age 40 years, and if estradiol was <17 pg/mL and FSH less than 11.2 IU/L. ACTH deficiency (ACTHD) was defined among survivors exposed to cranial RT if morning serum cortisol <5 µg/dL. Central precocious puberty (CPP) was defined as pubertal onset (i.e. Tanner 2 pubertal stage) before the age 8 years in girls and 9 years in boys.

Physical assessment

Height was converted into an age and gender adjusted z-score for participants aged <20 years. For participants ≥20 years, z-score data for age 20 years were used. Short stature was defined as a height z-score <-2. Depending on age at SJLIFE, obesity was defined as body mass index (weight/height^2) >30 kg/m^2 (≥ 20 years) or BMI z-score > 2 (< 20 years). BMD was assessed using dual x-ray absorptiometry (DEXA). Average volumetric trabecular BMD for lumbar vertebrae L1

and L2 was calculated and reported as age- and sex-specific z scores. Low BMD was defined as a z-score less <-2.[14]

Physiologic frailty was defined as meeting three or more of the following criteria: decreased lean muscle mass, decreased vitality, poor physical activity, slowness or weakness (Supplemental Table 1).[15] The 6-minute walk test was used to evaluate exercise tolerance.[16] Poor exercise tolerance was defined by less than 400 m of distance covered in six minutes. Hypertension, dyslipidemia, abnormal glucose metabolism and cardiomyopathy were defined as CTCAE grade 2 or higher.[12]

Psychosocial and neurocognitive assessment

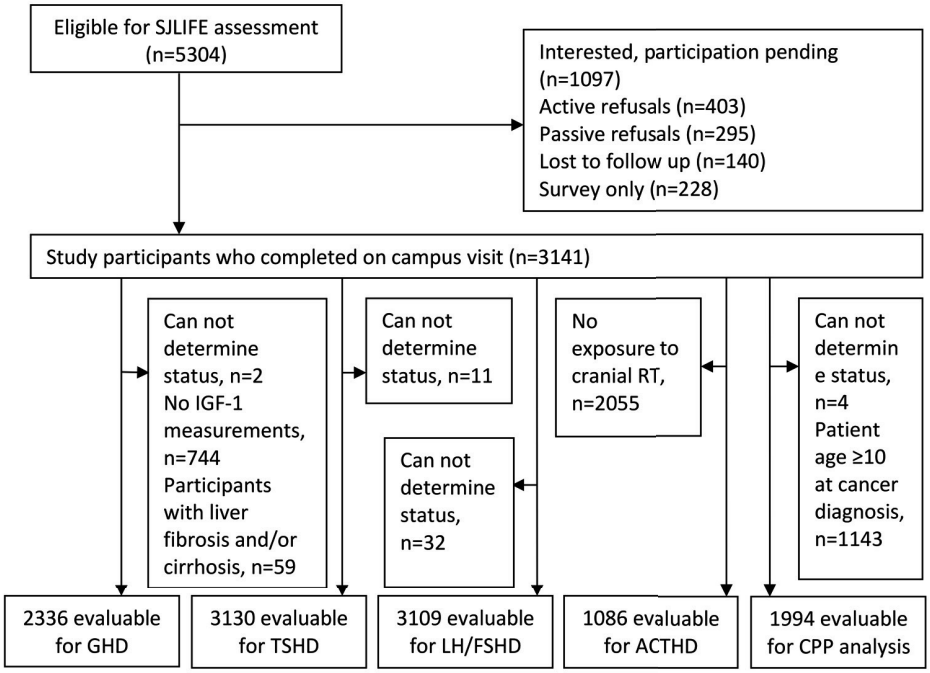
Health-related quality of life (HRQOL) was assessed using the physical (PCS) and mental (MCS) component summaries of the Medical Outcomes Study Short-Form 36.[17] Clinically meaningful impairment was assigned to those with scores ≤40, equivalent to a score one SD or more below the population mean of 50. Psychological distress was measured by the Brief Symptom Inventory (BSI-18), an 18-item questionnaire that provides a global measure of acute psychological distress, as well as subscale scores for anxiety, depression and somatization.[18] Psychological distress was defined as scores ≥63 for each subscale, representing the highest 10th percentile of population norms. In males, sexual dysfunction was considered present when sexually active individuals scored ≤25 points on an abbreviated 6-item version of the validated International Index of Erectile Function, embedded in the Men's Health Questionnaire (MHQ).[19] In addition, in non-sexually active males, responses to two ancillary questions of the MHQ were used to assess sexual dysfunction.[20] In sexually active females, sexual dysfunction was defined as a total score <10th percentile of population norms on the Sexual Functioning Questionnaire, embedded in the Women's Health Questionnaire (WHQ).[21] No ancillary questions were available in the WHQ to assess sexual dysfunction in sexually inactive females. Neurocognitive outcomes included memory, attention, processing speed and executive function, and were assessed with the instruments listed in Supplemental Table A2. For all four outcomes, a CTCAE grade 2 or higher was considered as impaired neurocognitive function.

Statistical analysis

Chi-squared, Fisher's exact, T- and Wilcoxon rank sum tests were used to compare demographic and treatment characteristics between participants and non-participants. Cumulative incidence was calculated using the Kaplan-Meier method and assigning the date of detection of an HP disorder as the date of occurrence and censoring participants without an event at last follow-up. Univariate log-binomial models were first used to examine associations between sociodemographic and treatment-related risk factors and HP disorders. For this analysis, participants with HP tumor involvement were excluded, as their tumor location made them particularly prone to develop HP disorders. Variables with p-value ≤0.1 were included in

multivariable log-binomial models for further analysis, without additional adjustments. Associations between HP disorders and physical, psychosocial and neurocognitive outcomes were also first examined in univariable log-binomial models. For this specific analysis, participants with HP tumor involvement were included. Variables with p-values ≤0.1 were included in multivariable models, together with predefined adjustments. SAS version 9.4 (SAS Institute, Cary, NC) was used for all analyses.

Figure 1. Flow diagram SJLIFE cohort



Abbreviations: ACTHD, ACTH deficiency; CPP, central precocious puberty; GHD, GH deficiency; IGF-1, insulin-like growth factor 1; LH/FSHD, LH/FSH deficiency; RT, radiation therapy; SJLIFE, St. Jude Lifetime Cohort Study; TSHD, TSH deficiency

Results

Study population

Among 5304 eligible survivors, 3141 (59.2%) completed an on campus visit as of June 30, 2016, and had evaluable data (Figure 1). Compared with non-participants (n=2163), study participants were more likely to be female, white, leukemia survivors, and have been diagnosed with cancer at an older age (Table 1). In addition, participants were more likely to have received chemotherapy

as well as alkylating agents and intrathecal chemotherapy, and less likely to have received cranial RT, compared to non-participants. Median age at assessment was 31.7 years (range, 7.5-65.1) and median time since cancer diagnosis was 24.1 years (range, 6.8-51.1). In 77 participants (2.5%), the CNS tumor involved the HP region (Supplemental Table 3). Treatment exposures included cranial RT in 1086 participants (34.6%) and alkylating agents in 1847 participants (58.8%).

Table 1. Sociodemographic and treatment characteristics of participants and non-participants

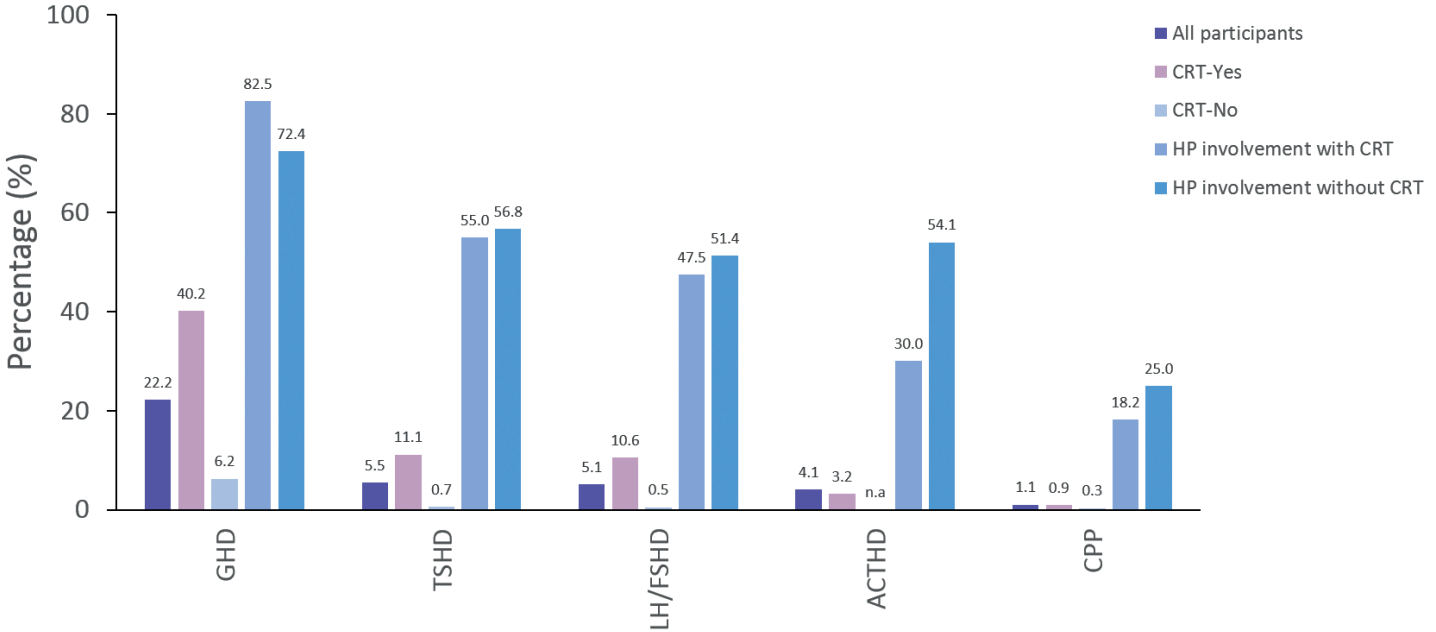
	Participants, N=3141		Non-participants, N=2163		
Variable	**No.**	**%**	**No.**	**%**	**P-value**
Sex					
Male	1638	52.15	1225	56.63	0.001
Female	1503	47.85	938	43.37	
Race/Ethnicity					
Non-Hispanic White	2565	81.66	1694	78.32	0.004
Non-Hispanic Black	465	14.80	363	16.78	
Other	111	3.53	106	4.90	
Age at tumor diagnosis (years)	Median (Range)		Median (Range)		
	6.81 (0-17.98)		5.98 (0-18.00)		<0.0001
Age at SJLIFE evaluation (years)	Median (Range)		Median (Range)		
	31.73 (7.52-65.13)		-	-	-
Primary tumor diagnosis					
Leukemia	1167	37.15	695	32.13	<0.0001
Lymphoma	558	17.77	357	16.50	
CNS tumor	352	11.21	304	14.05	
Craniopharyngioma	26	7.39	17	5.59	
Ependymoma	38	10.80	26	8.55	
Glial cell tumor	174	49.43	151	49.67	
Medulloblastoma	87	24.72	62	20.39	
Other CNS tumor	27	7.67	48	15.79	
Non-brain solid tumor of head and neck	203	6.46	183	8.46	
Other solid tumor	795	25.31	549	25.38	
Other	66	2.10	75	3.47	
HP involvement					
Yes	77	2.45	57	2.64	0.68
No	3064	97.55	2106	97.36	

Table 1. Continued

	Participants, N=3141		Non-participants, N=2163		
Variable	**No.**	**%**	**No.**	**%**	**P-value**
Stroke					
Yes	159	5.06	-	-	n.a.
No	2982	94.94	-	-	
Seizures					
Yes	382	12.16	-	-	n.a.
No	2759	87.84	-	-	
Hydrocephalus with shunt placement					
Yes	95	3.02	79	3.65	0.21
No	3046	96.98	2084	96.35	
HP RT dose (Gy)					
No cranial RT	2055	65.43	1533	70.87	<0.0001
1-19.9	399	12.70	183	8.46	
20-30	388	12.35	179	8.28	
>30	298	9.49	267	12.34	
Dose unknown	1	0.03	1	0.05	
Any chemotherapy					
Yes	2676	85.20	1757	81.23	0.0001
No	465	14.80	406	18.77	
Alkylating agents					
Yes	1847	58.80	1186	54.83	0.004
No	1294	41.20	977	45.17	
Intrathecal chemotherapy					
Yes	1273	40.53	803	37.12	0.01
No	1868	59.47	1360	62.88	

Abbreviations: CNS, central nervous system; Gy, gray; HP, hypothalamic-pituitary; n.a., not applicable; RT, radiation therapy; SJLIFE, St. Jude Lifetime Cohort Study

Figure 2. Prevalence of hypothalamic-pituitary disorders



Abbreviations: ACTHD, ACTH deficiency; CPP, central precocious puberty; CRT, cranial radiation therapy; GHD, GH deficiency; HP, hypothalamic-pituitary; LH/FSHD, LH/FSH deficiency; n.a., not applicable; TSHD, TSH deficiency.

Risk factors of hypothalamic-pituitary disorders

The estimated prevalence of all HP disorders is demonstrated in Figure 2. In the multivariable analysis, any HP dose of RT was associated with higher odds of GHD, TSHD and LH/FSHD, compared with no HP exposure to RT (Table 2). ACTHD was associated with cranial RT dose >30 Gy. Stroke was associated with higher odds for all four HP disorders. In addition, the multivariable analysis demonstrated significant associations between GHD and male sex, younger age at cancerdiagnosis, hydrocephalus with shunt placement, alkylating agents and intrathecal chemotherapy; TSHD was associated with white ethnicity, younger age at SJLIFE and seizures;

LH/FSHD was associated with male sex, white ethnicity, younger age at cancer diagnosis, hydrocephalus with shunt placement and alkylating agents; and ACTHD with younger age at SJLIFE and seizures. The limited number of participants with a history of CPP allowed only univariable analysis for this HP disorder. (Supplemental Table 4).

Cumulative incidence of hypothalamic-pituitary disorders

The estimated cumulative incidence at 40 years from cancer diagnosis is 38.7% (95%CI 34.8-42.9) for GHD, 6.1% (95% CI 4.8-7.7) for TSHD, 9.7% (95% CI 7.5-12.5) for LH/FSHD, and 3.6% (95%CI 2.5-5.3) for ACTHD (Supplemental Figure 1).

Physical health outcomes and hypothalamic-pituitary disorders

In total 24 of 519 (4.6%) participants with GHD, 163 of 172 (94.8%) participants with TSHD, 70 of 158 (44.3%) participants with LH/FSHD, and 44 of 45 (97.8%) participants with ACTHD were receiving hormone replacement therapy. As the number of eligible participants was low for ACTHD and CPP, only GHD, TSHD and untreated LH/FSHD were included in multivariable models for all health outcomes. Independent associations were observed between GHD and short stature, low BMD, frailty and poor exercise tolerance (Table 3); between TSHD and short stature and poor exercise tolerance; and between untreated LH/FSHD and obesity and low BMD.

Psychosocial and neurocognitive health outcomes, and hypothalamic-pituitary disorders

Significant associations were observed between TSHD and worse HRQOL in the physical domain (Table 4). Participants with untreated LH/FSHD had higher odds for sexual dysfunction, although this association was only significant for females. Participants with GHD and TSHD had higher odds of impaired memory and processing speed, compared to participants without these HP disorders.

Table 2. Multivariable logistic regression model for risk factors of hypothalamic-pituitary disorders

	GHD N=2267				TSHD N=3053				LH/FSHD N=3032				ACTHD N=1046			
Variable	**N (row%)**	**OR**	**95% CI**	**P-value**	**N (row%)**	**OR**	**95% CI**	**P-value**	**N (row%)**	**OR**	**95% CI**	**P-value**	**N (row%)**	**OR**	**95% CI**	**P-value**
Sex																
Male	271 (22.93)	1.00			-	-			95 (6.08)	1.00			24 (4.20)	1.00		
Female	194 (17.88)	0.76	0.60-0.96	0.02	-	-	-	-	25 (1.70)	0.29	0.18-0.47	<0.0001	9 (1.90)	0.46	0.20-1.04	0.06
Race/Ethnicity																
Non-Hispanic White	399 (21.63)	1.00			116 (4.66)	1.00			112 (4.53)	1.00			-	-		
Other	66 (15.64)	0.81	0.58-1.13	0.22	13 (2.31)	0.43	0.23-0.81	0.01	8 (1.43)	0.37	0.17-0.82	0.01	-	-	-	-
Age at tumor diagnosis (years)	Mean (SD)				Mean (SD)				Mean (SD)				Mean (SD)			
	6.12 (4.19)	0.92	0.89-0.94	<0.0001	6.53 (4.86)	0.97	0.93-1.02	0.20	6.65 (4.99)	0.95	0.90-0.99	0.02	-	-	-	-
Age at SJLIFE evaluation (years)	Mean (SD)				Mean (SD)				Mean (SD)				Mean (SD)			
	32.56 (8.21)	-	-	-	30.82 (7.40)	0.96	0.94-0.99	0.004	35.77 (9.60)	1.03	0.99-1.05	0.07	29.22 (5.75)	0.94	0.89-0.99	0.02
Stroke																
No	405 (18.93)	1.00			101 (3.48)	1.00			88 (3.05)	1.00			22 (2.34)	1.00		
Yes	60 (47.24)	1.76	1.15-2.72	0.01	28 (19.05)	2.52	1.47-4.33	0.001	32 (21.92)	3.45	2.02-5.91	<0.0001	11 (10.48)	3.12	1.32-7.42	0.01
Seizures																
No	368 (18.55)	1.00			89 (3.31)	1.00			82 (3.07)	1.00			19 (2.23)	1.00		
Yes	97 (34.28)	1.31	0.94-1.82	0.11	40 (11.05)	1.77	1.12-2.80	0.02	38 (10.58)	1.53	0.94-2.48	0.09	14 (7.25)	2.49	1.11-5.59	0.03

Table 2. continued

	GHD N=2267				TSHD N=3053				LH/FSHD N=3032				ACTHD N=1046			
Variable	**N (row%)**	**OR**	**95% CI**	**P-value**	**N (row%)**	**OR**	**95% CI**	**P-value**	**N (row%)**	**OR**	**95% CI**	**P-value**	**N (row%)**	**OR**	**95% CI**	**P-value**
Hydrocephalus with shunt placement																
No	431 (19.55)	1.00			111 (3.72)	1.00			103 (3.48)	1.00			26 (2.61)	1.00		
Yes	34 (54.84)	2.56	1.32-4.98	0.01	18 (25.71)	1.82	0.92-3.60	0.09	17 (24.29)	2.84	1.32-6.10	0.01	7 (14.00)	1.32	0.47-3.70	0.50
HP dose (Gy)																
No cranial RT	82 (6.24)	1.00			13 (0.65)	1.00			10 (0.50)	1.00				-	-	
1-19.9	103 (28.30)	4.02	2.85-5.67	<0.0001	31 (7.77)	12.86	6.61-25.03	<0.0001	19 (4.82)	7.49	3.40-16.52	<0.0001	5 (1.25)	1.00		
20-30	147 (41.53)	6.11	4.37-8.56	<0.0001	26 (6.74)	11.43	5.45-23.98	<0.0001	44 (11.37)	13.94	6.59-29.48	<0.0001	6 (1.55)	1.57	0.44-5.63	0.49
>30	132 (56.65)	22.95	15.50-33.97	<0.0001	59 (23.05)	33.53	17.59-63.90	<0.0001	46 (17.90)	28.84	13.79-60.32	<0.0001	22 (8.53)	4.41	1.38-14.11	0.01
Alkylating agents																
No	148 (16.25)	1.00				-			31 (2.56)	1.00				-	-	
Yes	317 (23.38)	1.41	1.09-1.83	0.01		-	-	-	89 (4.89)	1.93	1.20-3.11	0.01	-	-	-	-
Intrathecal chemotherapy																
No	180 (14.91)	1.00				-			-	-			23 (5.61)	1.00		
Yes	285 (26.89)	2.24	1.65-3.04	<0.0001		-	-	-	-	-	-	-	10 (1.57)	1.00	0.33-3.03	0.99

Abbreviations: ACTHD, ACTH deficiency; CI, confidence interval; GHD, GH deficiency; Gy, gray; HP, hypothalamic-pituitary; LH/FSHD, LH/FSH deficiency; OR, odds ratio; RT, radiation therapy; SJLIFE, St. Jude Lifetime Cohort Study; TSHD, TSH deficiency

Table 3. Multivariable logistic regression model for hypothalamic-pituitary disorders and physical health outcomes

		GHD					TSHD					Untreated LH/FSHD				
	Clinical outcome (Yes)	GHD	No GHD	Multivariable analysis			TSHD	No TSHD	Multivariable analysis			LH/ FSHD	No LH/ FSHD	Multivariable analysis		
Variable	(N,%)	(N, %)	(N, %)	OR	95% CI	P-value	(N, %)	(N, %)	OR	95% CI	P-value	(N, %)	(N, %)	OR	95% CI	P-value
Physical health outcomes																
Short stature (n=2231)	209 (9.37)	105 (23.08)	104 (5.86)	3.50	2.54-4.83	<0.0001	33 (28.21)	176 (8.33)	1.90	1.16-3.10	0.01	16 (20.51)	193 (8.96)	0.95	0.50-1.79	0.87
Obesity (n=2210)	825 (37.33)	199 (44.52)	626 (35.51)	1.20	0.94-1.54	0.15	48 (41.38)	777 (37.11)	0.83	0.54-1.27	0.39	49 (63.64)	776 (36.38)	2.62	1.56-4.41	0.0003
Low BMD (n=2035)	521 (25.60)	164 (40.49)	357 (21.90)	2.16	1.68-2.78	<0.0001	49 (47.57)	472 (24.43)	1.54	0.98-2.42	0.06	32 (55.17)	489 (24.73)	2.40	1.35-4.26	0.003
Hypertension (n=2203)	352 (15.98)	-	-	-	-	-	16 (13.91)	336 (16.09)	1.09	0.60-1.97	0.78	19 (24.68)	333 (15.66)	1.13	0.61-2.08	0.70
Dyslipidemia (n=2150)	112 (5.21)	-	-	-	-	-	7 (6.25)	105 (5.15)	1.31	0.56-3.07	0.53	9 (11.84)	103 (4.97)	1.49	0.67-3.30	0.32
Abnormal glucose metabolism (n=2265)	140 (6.18)	40 (7.92)	100 (5.68)	1.42	0.92-2.18	0.11	13 (7.98)	127 (6.04)	1.31	0.68-2.54	0.43	-	-	-	-	-
Frailty (n=2064)	118 (5.72)	41 (9.74)	77 (4.69)	1.87	1.21-2.91	0.01	14 (13.46)	104 (5.31)	1.87	0.96-3.65	0.07	9 (13.04)	109 (5.46)	1.57	0.71-3.50	0.26
Poor exercise tolerance (n=2087)	170 (8.15)	49 (11.86)	121 (7.23)	1.51	1.02-2.23	0.04	18 (18.18)	152 (7.65)	2.15	1.17-3.95	0.01	11 (16.42)	159 (7.87)	1.44	0.69-3.03	0.33
Cardiomyopathy (n=2277)	139 (6.10)	21 (4.15)	118 (6.66)	0.80	0.48-1.34	0.40	4 (2.45)	135 (6.39)	0.87	0.30-2.54	0.80	-	-	-	-	-

Short stature was adjusted for craniospinal radiotherapy and stem cell transplantation; increased BMI was adjusted for sex, ethnicity/race, age at SJLIFE, cranial radiation therapy and age at cancer diagnosis; low BMD was adjusted for obesity (i.e. BMI >30kg/m2), prednisone equivalent dose and total body irradiation; hypertension was adjusted for sex, age at SJLIFE, ethnicity/race, obesity and age at cancer diagnosis; dyslipidemia was adjusted for sex, age at SJLIFE, ethnicity/race, obesity and age at cancer diagnosis; abnormal glucose metabolism was adjusted for sex, age at SJLIFE, ethnicity/race, obesity and age at cancer diagnosis; poor exercise tolerance was adjusted for sex, age at SJLIFE and obesity; frailty was adjusted for age at cancer diagnosis and smoking status; cardiomyopathy was adjusted for sex, age at SJLIFE, ethnicity/race, obesity, previous anthracycline use and chest irradiation

Abbreviations: BMD, bone mineral density; BMI; body mass index; CI, confidence interval; GHD, GH deficiency; LH/FSHD, LH/FSH deficiency; OR, odds ratio; TSHD, TSH deficiency

Table 4. Multivariable logistic regression model for hypothalamic-pituitary and psychosocial and neurocognitive health outcomes

		GHD					TSHD					Untreated LH/FSHD				
	Clinical outcome (Yes)	GHD	No GHD	Multivariable analysis			TSHD	No TSHD	Multivariable analysis			LH/ FSHD	No LH/ FSHD	Multivariable analysis		
Variable	(N, %)	(N, %)	(N, %)	OR	95% CI	P-value	(N, %)	(N, %)	OR	95% CI	P-value	(N, %)	(N, %)	OR	95% CI	P-value
Psychosocial health outcomes																
PCS (n=2036)	359 (17.63)	84 (20.10)	275 (17.00)	1.26	0.91-1.75	0.16	31 (29.52)	328 (16.99)	2.38	1.45-3.92	0.0007	18 (24.66)	341 (17.37)	1.03	0.57-1.89	0.91
GSI (n=2051)	291 (14.19)	-	-	-	-	-	14 (9.86)	277 (14.51)	0.89	0.49-1.61	0.70	-	-	-	-	-
Anxiety (n=2052)	242 (11.79)	-	-	-	-	-	9 (6.34)	233 (12.20)	0.68	0.33-1.38	0.29	-	-	-	-	-
Depression (n=1992)	300 (15.06)	-	-	-	-	-	-	-	-	-	-	17 (23.94)	283 (14.73)	1.75	0.97-3.14	0.06
Psychosexual dysfunction (n=1337)	438 (32.76)	104 (40.00)	334 (31.01)	1.29	0.96-1.74	0.10	36 (46.75)	402 (31.90)	1.44	0.87-2.38	0.15	25 (54.35)	413 (31.99)	2.05	1.09-3.83	0.03
Male psychosexual dysfunction (n=645)	177 (27.44)	48 (33.33)	129 (25.75)	1.31	0.86-1.99	0.20	-	-	-	-	-	14 (42.42)	163 (26.63)	2.06	0.98-4.35	0.06
Female psychosexual dysfunction (n=692)	261 (37.72)	56 (48.28)	205 (35.59)	1.40	0.90-2.16	0.13	23 (50.00)	238 (36.84)	1.13	0.58-2.21	0.72	250 (36.82)	11 (84.62)	6.91	1.43-33.42	0.02

Table 4. Continued

		GHD					TSHD					Untreated LH/FSHD				
	Clinical outcome (Yes)	GHD	No GHD	Multivariable analysis			TSHD	No TSHD	Multivariable analysis			LH/ FSHD	No LH/ FSHD	Multivariable analysis		
Variable	**(N, %)**	**(N, %)**	**(N, %)**	**OR**	**95% CI**	**P-value**	**(N, %)**	**(N, %)**	**OR**	**95% CI**	**P-value**	**(N, %)**	**(N, %)**	**OR**	**95% CI**	**P-value**
Neurocognitive health outcomes																
Memory (n=1370)	290 (21.17)	85 (37.78)	205 (17.90)	1.74	1.21-2.52	0.003	34 (54.84)	256 (19.57)	3.46	1.91-6.27	<0.0001	15 (31.25)	275 (20.80)	0.56	0.27-1.15	0.11
Attention (n=1403)	255 (18.18)	62 (24.12)	193 (16.84)	1.12	0.75-1.67	0.57	27 (30.68)	228 (17.34)	1.63	0.95-2.79	0.08	-	-	-	-	-
Processing speed (n=1173)	84 (7.16)	38 (16.96)	46 (4.85)	1.80	1.01-3.21	0.05	19 (25.68)	65 (5.91)	2.12	1.07-4.21	0.03	-	-	-	-	-
Executive function (n=1194)	275 (23.03)	79 (34.05)	196 (20.37)	1.14	0.77-1.67	0.52	33 (41.25)	242 (21.72)	1.55	0.90-2.66	0.11					

PCS was adjusted for sex, age at SJLIFE and cranial radiation therapy; all parameters of emotional distress (i.e. GSI, anxiety and depression) were adjusted for age at SJLIFE, sex, cranial radiation therapy, excessive alcohol use, illicit drug use and smoking status; psychosexual dysfunction was adjusted for age at SJLIFE and ethnicity/race; all four neurocognitive health outcomes were adjusted for cranial radiation therapy. Initially, the interaction term cranial radiation therapy dose and hypothalamic-pituitary disorders was included in the model, however the P-value was >0.1, suggesting that this interaction term should not be included in the final model. Abbreviations: CI, confidence interval; GHD, GH deficiency; GSI, Global Severity Index; LH/FSHD, LH/FSH deficiency; MCS, Mental Component Summary; OR, odds ratio; PCS, Physical Component Summary; TSHD, TSH deficiency

Discussion

Using a large, clinically and systematically assessed cohort of long-term adult survivors of childhood cancer, this study characterized prevalence, risk factors and co-morbidities associated with HP disorders in childhood cancer survivors. Our study findings identify novel treatment and clinical factors such as alkylating agents and CNS injury that contribute to HP dysfunction in adult survivors of childhood cancer. HP disorders were also independently associated with impaired physical, sexual and neurocognitive function. Importantly, as HP disorders were often untreated in our population, hormonal replacement therapy represents an intervention that may improve well-being.

Cranial RT is a well-established risk factor for HP disorders.[7,8] Systematic assessment of HP function and specific dosimetry data for the HP region in this cohort, facilitated identification of lower RT dose-relationships for TSHD and LH/FSHD. These HP disorders are generally considered to occur at RT doses >30 Gy, and screening is often recommended after exposure to high-dose RT.[9] Studies supporting these recommendations often do not include comparison groups without RT exposure who received evaluation of their endocrine status, limiting identification of exact dose-response relationships.[10,22] Our study results suggest that screening for TSHD and LH/FSHD at lower RT doses should not be restricted to GHD, though our results should be validated in other cohorts. Unfortunately, we could not establish accurate dose-response relationships for ACTHD, as the sensitivity for cortisol measurements is too low to use as a screening modality in large cohort studies.

The contribution of chemotherapy to risk of HP injury remains controversial.[2] HP dysfunction following chemotherapy, in the absence of exposure to cranial RT, has only been reported in small case series.[23-25] However, chemotherapy has been observed to add to risk conferred by cranial RT, although the exact mechanism is unclear.[5,26] Our study demonstrated a significant association between alkylating agents and GHD, and LH/FSHD. In addition, intrathecal chemotherapy was significantly associated with GHD. Intrathecal chemotherapy has well established potential for CNS toxicity, but has not previously been linked to the development of HP dysfunction.[23,27] Future studies are needed to elucidate the pathophysiology of chemotherapy induced HP injury.

HP disorders following traumatic brain injury in children have been described with a prevalence ranging from 5% to 57%.[28] Pathophysiological mechanisms for HP dysfunction in these children may result from ischemia of the normally highly vascularized pituitary gland associated with low cerebral perfusion.[29] Other possible explanations include direct compression or mechanical trauma to the pituitary gland.[30,31] In our study, we observed significant associations between HP disorders and conditions associated with CNS insult such as stroke, seizures and hydrocephalus with shunt placement. Unfortunately, whether the onset of HP disorders preceded the CNS insult

could not be assessed with certainty. Therefore, it is unknown if these associations are causal or if they just reflect mutual etiological risk factors (i.e. cranial RT or CNS tumor).

In our cohort, the prevalence of HP disorders was highest among participants with tumor involvement in the HP region, similar to previous reports including children with tumors arising near the pituitary gland, hypothalamus or optic pathways, such as low-grade glioma or craniopharyngioma.[8,32,33] Secondly, the prevalence of HP dysfunction was high among participants with previous cranial RT exposure. GHD was the most common HP disorder, followed by TSHD, LH/FSHD, and ACTHD, respectively; a well-known hierarchical pattern of post-RT hypopituitarism.[7,33] As expected, CPP was primarily observed in participants with HP tumor involvement, and at similar percentages between 26% and 29% as reported in literature in patients with HP tumor location.[6,33] Although CPP has been reported at a rate of 6.6% after RT in patients without HP tumor involvement, the occurrence of CPP in our cohort was very low (i.e. <1%) for reasons that are unclear.[6]

This study is among the first to systematically assess the prevalence of HP disorders in survivors of childhood cancer with tumors that do not involve the HP region and those not previously exposed to cranial RT. Among these, a small proportion demonstrated HP dysfunction with GHD representing the most prevalent condition in 6%. In these cases, other potential mechanisms may result in HP-damage such as leukemic infiltration, hydrocephalus with shunt placement or other CNS insult.[34,35] As the diagnosis GHD was based on low IGF-1 levels, a non-standard diagnostic test, there is a possibility for false positive GHD cases among these participants. Although validation is required, our results emphasize the importance of monitoring the growth and (pubertal) development of all survivors and having a low threshold for evaluation and endocrine referral of survivors with clinical signs of HP disorders, especially for GHD.

In our study, HP disorders significantly affected clinically assessed physical function and self-reported HRQOL in the physical domain, but not emotional well-being. Short stature, low BMD, frailty and poor exercise tolerance were physical factors associated with GHD. Similar associations have been previously reported in survivors of childhood cancer, especially in studies comparing GH treated and untreated survivors.[10,36,37] In the previous SJLIFE report, untreated LH/FSHD was also associated with low BMD, likely reflecting the known effect of decreased sex steroid levels on bone health.[10] The association between untreated LH/FSHD and obesity may be bidirectional; representing a cause or consequence, as testosterone levels also tend to be lower in obese men.[38] Unexpectedly, we did not observe associations between adverse metabolic outcomes and HP disorders, despite the large proportion of patients who did not receive hormonal replacement therapy.[39,40] Interestingly, untreated LH/FSHD was associated with impaired sexual dysfunction. Both females and males with LH/FSHD tended to report sexual dysfunction more frequently, although the association was only significant for females. This is surprising, as low testosterone

levels in a previous SJLIFE report, were strongly associated with impaired sexual functioning.[20] It is possible the previous finding resulted from low testosterone levels related to Leydig cell failure, rather than central HP damage.

Endocrine disorders have been shown to contribute to neurocognitive impairment in survivors of childhood cancer, but associations with specific endocrine disorders have not been previously identified.[41] Our study revealed independent associations between impaired memory and processing speed and GHD and TSHD. Impaired neurocognitive functioning, especially memory, has been observed in small studies including GH deficient patients from the general population.[42] In addition, hypothyroidism impairs neurocognitive development during childhood or neurocognitive functioning in adulthood, although this evidence originates from studies of primary and congenital forms of hypothyroidism.[43] While the significant associations between HP disorders and impaired neurocognitive functioning are concerning, these results may be the consequence of mutual risk factors, rather than demonstrating causal relationships.[44] These provocative results should be validated in other cohorts.

The current study has several limitations. HP disorders were defined with screening modalities that often require additional testing to confirm the diagnosis. This may have resulted in both false positive and false negative diagnoses. Also, the proportions of risk- and non-risk based screened participants differ among different HP-axes, which limits the ability to compare overall prevalence and cumulative incidence between different HP-axes. In addition, temporal onset of HP disorders in relation to CNS injury could not be determined. This has limited our ability to establish causal relationships between CNS injury and HP disorders.

In conclusion, our study demonstrates that survivors of childhood cancer are at increased risk for HP disorders predominantly related to primary cancer location in HP region and cranial RT, but also after specific treatment modalities that extend beyond cranial RT, and conditions associated with CNS injury. Survivors exposed to low dose cranial RT, seem to be at risk for HP dysfunction including GHD and to a lesser extent TSHD and LH/FSHD. Survivors with HP disorders experience more adverse physical, sexual and neurocognitive outcomes compared to survivors without HP disorders. Challenges in current follow-up care include providing adequate screening and hormone replacement therapy of HP disorders for all survivors at risk, as well as attention to the physical and psychosexual effects of these conditions.

References

1. Bhakta N, Liu Q, Ness KK, et al. The cumulative burden of surviving childhood cancer: an initial report from the St Jude Lifetime Cohort Study (SJLIFE). *Lancet.* 2017;390(10112):2569-2582.
2. Crowne E, Gleeson H, Benghiat H, Sanghera P, Toogood A. Effect of cancer treatment on hypothalamic-pituitary function. *Lancet Diabetes Endocrinol.* 2015;3(7):568-576.
3. Chemaitilly W, Cohen LE. DIAGNOSIS OF ENDOCRINE DISEASE: Endocrine late-effects of childhood cancer and its treatments. *Eur J Endocrinol.* 2017;176(4):R183-R203.
4. Chemaitilly W, Cohen LE, Mostoufi-Moab S, et al. Endocrine Late Effects in Childhood Cancer Survivors. *J Clin Oncol.* 2018;36(21):2153-2159.
5. Gleeson HK, Stoeter R, Ogilvy-Stuart AL, Gattamaneni HR, Brennan BM, Shalet SM. Improvements in final height over 25 years in growth hormone (GH)-deficient childhood survivors of brain tumors receiving GH replacement. *J Clin Endocrinol Metab.* 2003;88(8):3682-3689.
6. Chemaitilly W, Merchant TE, Li Z, et al. Central precocious puberty following the diagnosis and treatment of paediatric cancer and central nervous system tumours: presentation and long-term outcomes. *Clin Endocrinol (Oxf).* 2016;84(3):361-371.
7. Clement SC, Schouten-van Meeteren AY, Boot AM, et al. Prevalence and Risk Factors of Early Endocrine Disorders in Childhood Brain Tumor Survivors: A Nationwide, Multicenter Study. *J Clin Oncol.* 2016;34(36):4362-4370.
8. Armstrong GT, Liu Q, Yasui Y, et al. Long-term outcomes among adult survivors of childhood central nervous system malignancies in the Childhood Cancer Survivor Study. *J Natl Cancer Inst.* 2009;101(13):946-958.
9. Sklar CA, Antal Z, Chemaitilly W, et al. Hypothalamic-Pituitary and Growth Disorders in Survivors of Childhood Cancer: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2018;103(8):2761-2784.
10. Chemaitilly W, Li Z, Huang S, et al. Anterior hypopituitarism in adult survivors of childhood cancers treated with cranial radiotherapy: a report from the St Jude Lifetime Cohort study. *J Clin Oncol.* 2015;33(5):492-500.
11. Hudson MM, Ness KK, Nolan VG, et al. Prospective medical assessment of adults surviving childhood cancer: study design, cohort characteristics, and feasibility of the St. Jude Lifetime Cohort study. *Pediatr Blood Cancer.* 2011;56(5):825-836.
12. Hudson MM, Ehrhardt MJ, Bhakta N, et al. Approach for Classification and Severity Grading of Long-term and Late-Onset Health Events among Childhood Cancer Survivors in the St. Jude Lifetime Cohort. *Cancer Epidemiol Biomarkers Prev.* 2017;26(5):666-674.
13. Stovall M, Weathers R, Kasper C, et al. Dose reconstruction for therapeutic and diagnostic radiation exposures: use in epidemiological studies. *Radiat Res.* 2006;166(1 Pt 2):141-157.
14. Cann CE, Genant HK, Kolb FO, Ettinger B. Quantitative computed tomography for prediction of vertebral fracture risk. *Bone.* 1985;6(1):1-7.
15. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci.* 2001;56(3):M146-156.
16. Enright PL. The six-minute walk test. *Respir Care.* 2003;48(8):783-785.
17. Waren JE , Kosinski M , Dewey JE . How to Score Version 2 of the SF-36 Health Survey. Lincoln, RI: QualityMetric Inc; 2000.
18. Derogatis L. Brief Symptom Inventory (BSI): Administration, Scoring, and Procedures Manual. NCS Pearson: Minneapolis, MN, USA; 2000.

19. Cappelleri JC, Rosen RC, Smith MD, Mishra A, Osterloh IH. Diagnostic evaluation of the erectile function domain of the International Index of Erectile Function. *Urology.* 1999;54(2):346-351.

20. van Iersel L, Li Z, Chemaitilly W, et al. Erectile Dysfunction in Male Survivors of Childhood Cancer. *JAMA Oncol.* 2018;4(11):1613-1616.

21. Syrjala, K.L., et al., Sexual Function Measurement and Outcomes in Cancer Survivors and Matched Controls. The Journal of Sex Research, 2000. 37(3): p. 213-225.

22. Constine LS, Woolf PD, Cann D, et al. Hypothalamic-pituitary dysfunction after radiation for brain tumors. *N Engl J Med.* 1993;328(2):87-94.

23. Rose SR, Schreiber RE, Kearney NS, et al. Hypothalamic dysfunction after chemotherapy. *J Pediatr Endocrinol Metab.* 2004;17(1):55-66.

24. Voorhess ML, Brecher ML, Glicksman AS, et al. Hypothalamic-pituitary function of children with acute lymphocytic leukemia after three forms of central nervous system prophylaxis. A retrospective study. *Cancer.* 1986;57(7):1287-1291.

25. Birkebaek NH, Fisker S, Clausen N, Tuovinen V, Sindet-Pedersen S, Christiansen JS. Growth and endocrinological disorders up to 21 years after treatment for acute lymphoblastic leukemia in childhood. *Med Pediatr Oncol.* 1998;30(6):351-356.

26. Spoudeas HA, Hindmarsh PC, Matthews DR, Brook CG. Evolution of growth hormone neurosecretory disturbance after cranial irradiation for childhood brain tumours: a prospective study. *J Endocrinol.* 1996;150(2):329-342.

27. Hasle H, Helgestad J, Christensen JK, Jacobsen BB, Kamper J. Prolonged intrathecal chemotherapy replacing cranial irradiation in high-risk acute lymphatic leukaemia: long-term follow up with cerebral computed tomography scans and endocrinological studies. *Eur J Pediatr.* 1995;154(1):24-29.

28. Casano-Sancho P. Pituitary dysfunction after traumatic brain injury: are there definitive data in children? *Arch Dis Child.* 2017;102(6):572-577.

29. Ghigo E, Masel B, Aimaretti G, et al. Consensus guidelines on screening for hypopituitarism following traumatic brain injury. *Brain Inj.* 2005;19(9):711-724.

30. Kelly DF, Gonzalo IT, Cohan P, Berman N, Swerdloff R, Wang C. Hypopituitarism following traumatic brain injury and aneurysmal subarachnoid hemorrhage: a preliminary report. *J Neurosurg.* 2000;93(5):743-752.

31. Dusick JR, Wang C, Cohan P, Swerdloff R, Kelly DF. Pathophysiology of hypopituitarism in the setting of brain injury. *Pituitary.* 2012;15(1):2-9.

32. Kendall-Taylor P, Jonsson PJ, Abs R, et al. The clinical, metabolic and endocrine features and the quality of life in adults with childhood-onset craniopharyngioma compared with adult-onset craniopharyngioma. *Eur J Endocrinol.* 2005;152(4):557-567.

33. Gan HW, Phipps K, Aquilina K, Gaze MN, Hayward R, Spoudeas HA. Neuroendocrine Morbidity After Pediatric Optic Gliomas: A Longitudinal Analysis of 166 Children Over 30 Years. *J Clin Endocrinol Metab.* 2015;100(10):3787-3799.

34. Quigg TC, Haddad NG, Buchsbaum JC, Shih CS. Hypothalamic obesity syndrome: rare presentation of CNS+ B-cell lymphoblastic lymphoma. *Pediatr Blood Cancer.* 2012;59(5):930-933.

35. Merchant TE, Rose SR, Bosley C, Wu S, Xiong X, Lustig RH. Growth hormone secretion after conformal radiation therapy in pediatric patients with localized brain tumors. *J Clin Oncol.* 2011;29(36):4776-4780.

36. Cohen LE, Gordon JH, Popovsky EY, et al. Bone density in post-pubertal adolescent survivors of childhood brain tumors. *Pediatr Blood Cancer.* 2012;58(6):959-963.

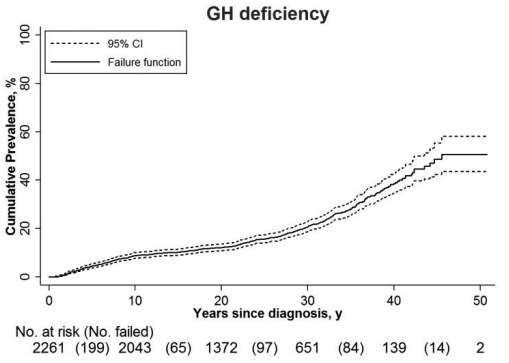
37. Tamhane S, Sfeir JG, Kittah NEN, et al. GH Therapy in Childhood Cancer Survivors: A Systematic Review and Meta-Analysis. *J Clin Endocrinol Metab.* 2018;103(8):2794-2801.

38. Kelly DM, Jones TH. Testosterone and obesity. *Obes Rev.* 2015;16(7):581-606.
39. Murray RD, Darzy KH, Gleeson HK, Shalet SM. GH-deficient survivors of childhood cancer: GH replacement during adult life. *J Clin Endocrinol Metab.* 2002;87(1):129-135.
40. Follin C, Thilen U, Osterberg K, Bjork J, Erfurth EM. Cardiovascular risk, cardiac function, physical activity, and quality of life with and without long-term growth hormone therapy in adult survivors of childhood acute lymphoblastic leukemia. *J Clin Endocrinol Metab.* 2010;95(8):3726-3735.
41. Cheung YT, Brinkman TM, Li C, et al. Chronic Health Conditions and Neurocognitive Function in Aging Survivors of Childhood Cancer: A Report from the Childhood Cancer Survivor Study. *J Natl Cancer Inst.* 2018;110(4):411-419.
42. Nyberg F, Hallberg M. Growth hormone and cognitive function. *Nat Rev Endocrinol.* 2013;9(6):357-365.
43. Dugbartey AT. Neurocognitive aspects of hypothyroidism. *Arch Intern Med.* 1998;158(13):1413-1418.
44. Krull KR, Li C, Phillips NS, et al. Growth hormone deficiency and neurocognitive function in adult survivors of childhood acute lymphoblastic leukemia. *Cancer.* 2019.

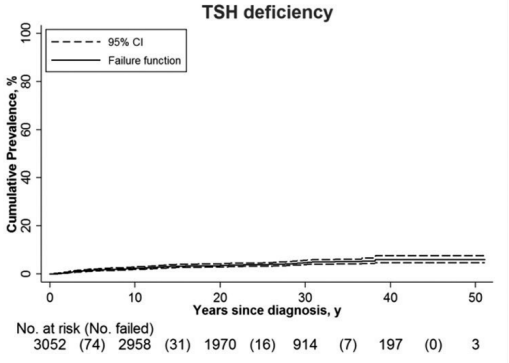
Supplementary material

Supplemental Figure 1. Cumulative incidence of (A) GH deficiency, (B) TSH deficiency, (C) LH/FSH deficiency, and (D) ACTH deficiency from cancer diagnosis

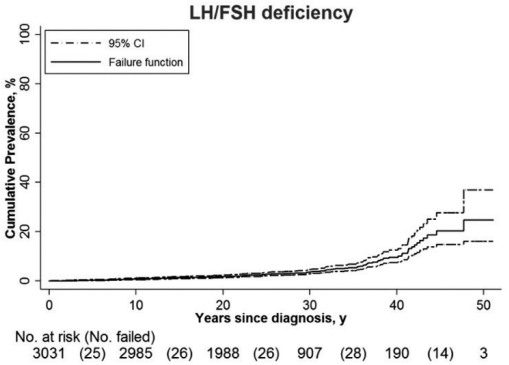
(A)



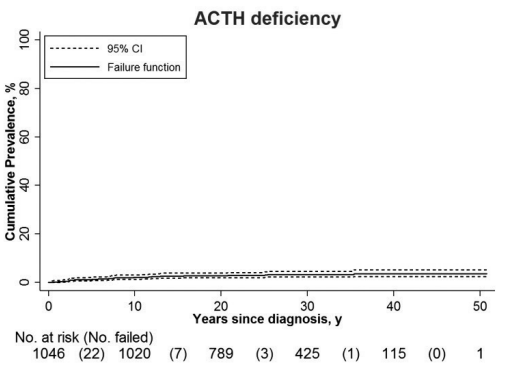
(B)



(C)



(D)



Supplemental Table 1. Criteria used to define frailty in the SJLIFE cohort

<table>
<tr><th>Frailty Component</th><th>St. Jude Lifetime Cohort Criteria</th></tr>
<tr><td>Decreased lean muscle mass</td><td>Lean muscle mass by dual x-ray absorptiometry <-1 age and sex specific SDS when compared to data from a national sample (National Health and Nutrition Examination Survey (NHANES)).[a]</td></tr>
<tr><td>Decreased vitality</td><td>Score ≤40 (1 SDS, based on a standard normal distribution, this represents approximately the lowest 6.7% of the general population) on the Vitality Subscale of the Medical Outcomes Survey Short Form 36 (SF-36).[b]</td></tr>
<tr><td>Poor physical activity</td><td>Expended <383 Kcal per week (males) or <270 Kcal per week (females) during Leisure Time Physical Activity based on the NHANES Physical Activity Questionnaire.[c,d]</td></tr>
<tr><td>Walking speed (slowness)</td><td>Females <159 and males <173 centimeters tall were classified as slow if they took ≥7 seconds, and females ≥159 and males ≥173 centimeters tall were classified as slow if they took ≥6 seconds to walk 15 feet at their usual pace.[e]</td></tr>
<tr><td>Hand grip strength (weakness)</td><td>Hand grip strength stratified by body mass index and sex[e]
<table>
<tr><th colspan="2">Males</th><th colspan="2">Females</th></tr>
<tr><th>BMI</th><th>Cut point</th><th>BMI</th><th>Cut point</th></tr>
<tr><td>≤ 24 kg/m2</td><td>≤29 kg</td><td>≤ 23 kg/m2</td><td>≤17 kg</td></tr>
<tr><td>24.1-26 kg/m2</td><td>≤30 kg</td><td>23.1-26 kg/m2</td><td>≤17.3 kg</td></tr>
<tr><td>26.1-28 kg/m2</td><td>≤30 kg</td><td>26.1-29 kg/m2</td><td>≤18 kg</td></tr>
<tr><td>> 28 kg/m2</td><td>≤32 kg</td><td>> 29 kg/m2</td><td>≤21 kg</td></tr>
</table></td></tr>
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[a] Kelly TL, Wilson KE, Heymsfield SB: Dual energy X-Ray absorptiometry body composition reference values from NHANES. PLoS One 4:e7038, 2009

[b] Ware JE, Jr., Sherbourne CD: The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 30:473-83, 1992

[c] Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey Physical Activity and Physical Fitness - PAQ 2007. Available at: http://www.cdc.gov/nchs/data/nhanes/nhanes_07_08/paq07_08_eng.pdf.

[d] Ainsworth BE, Haskell WL, Herrmann SD, et al: 2011 Compendium of Physical Activities: a second update of codes and MET values. Med Sci Sports Exerc 43:1575-81, 2011

[e] Fried LP, Tangen CM, Walston J, et al: Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 56:M146-56, 2001

Supplemental Table 2. Neurocognitive measures and assessment instruments

Neurocognitive outcome	Assessment instrument
Memory	California Verbal Learning Test-II: Total Learning, Short-Delay Free Recall and Long-Delay Free Recall[a]
Attention	Trail Making Test Part A[b], Conners' Continuous Performance Test-II Omissions and Variability[c], Digit Span Forward subtest of the Wechsler Adult Intelligence Scale-III (WAIS-III)[d]
Processing speed	Coding and Symbol Search subtests of the WAIS-III[d], Continuous Performance Test-II Hit Rate[c]
Executive function	Trail Making Test Part B[b], Controlled Oral Word Association Test[b], Digit Span Backward subtest of the WAIS-III[d]

[a] Delis D, Kramer J, Kaplan E, et al. California Verbal Learning Test. Second ed. San Antonio, TX, Psychological Coorporation, 2000.
[b] Strauss E, Sherman E, Spreen O. A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary. Third ed. New York, NY, Oxford University Press, 2006.
[c] Conners C. Conners' Continuous Performance Test II. North Tonawanda, NY: MultiHealth Systems, 2001.
[d] Wechsler D. Wechsler Abbreviated Scale of Intelligence. San Antonio, TX. Psychological Corporation, 1999.

Supplemental Table 3. Sociodemographic and treatment characteristics of participants with tumor involvement of the hypothalamic-pituitary (HP) region

	Participants, N=77	
Variable	**No.**	**%**
Sex		
Male	44	57.14
Female	33	42.86
Race/Ethnicity		
Non-Hispanic White	63	81.82
Non-Hispanic Black	12	15.58
Other	2	2.60
Age at tumor diagnosis (years)	Median (Range)	
	8.27 (0.43-17.73)	
Age at SJLIFE (years)	Median (Range)	
	25.31 (19.21-40.51)	
Primary tumor diagnosis		
Craniopharyngioma	26	33.77
Glial cell tumors	46	59.74
Other CNS tumor	5	6.49
Stroke		

Supplemental Table 3. Continued

	Participants, N=77	
Variable	**No.**	**%**
Yes	12	15.58
No	65	84.42
Seizures		
Yes	20	25.97
No	57	74.03
Hydrocephalus with shunt placement		
Yes	25	32.47
No	52	67.53
HP dose (Gy)		
No cranial RT	37	48.05
1-19.9	-	-
20-30	-	-
>30	40	51.95
Alkylating agents		
Yes	4	5.19
No	73	94.81
Intrathecal chemotherapy		
Yes	-	-
No	77	100

Abbreviations: CNS, central nervous system; Gy, gray; HP, hypothalamic-pituitary; RT, radiation therapy; SJLIFE, St. Jude Lifetime Cohort Study

Supplemental Table 4. Univariable logistic regression for risk factors of central precocious puberty

Variable	CPP, N=1994		P-value
	Yes N (%)	No N (%)	
Sex			
Male	10 (47.62)	1024 (51.90)	0.70
Female	11 (52.38)	949 (48.10)	
Race/Ethnicity			
Non-Hispanic White	14 (66.67)	1630 (82.62)	0.02
Non-Hispanic Black	4 (19.05)	281 (14.24)	
Other	3 (14.29)	62 (3.14)	
Age at tumor diagnosis (years)	Mean (SD)	Mean (SD)	
	4.17 (2.08)	4.37 (2.68)	0.87
Age at SJLIFE (years)	Mean (SD)	Mean (SD)	
	26.06 (3.99)	30.99 (8.79)	0.01
HP involvement			
Yes	10 (47.62)	36 (1.82)	<0.0001
No	11 (52.38)	1937 (98.18)	
Stroke			
Yes	4 (19.05)	105 (5.32)	0.02
No	17 (80.95)	1868 (94.68)	
Seizures			
Yes	7 (33.33)	254 (12.87)	0.01
No	14 (66.67)	1719 (87.13)	
Hydrocephalus with shunt placement			
Yes	4 (19.05)	51 (2.58)	0.002
No	17 (80.95)	1922 (97.42)	
HP dose (Gy)			
No cranial RT	10 (47.62)	1221 (61.89)	0.004
1-19.9	2 (9.52)	267 (13.53)	
20-30	2 (9.52)	309 (15.66)	
>30	7 (33.33)	175 (8.87)	
Dose unknown	-	1 (0.05)	
Alkylating agents			
Yes	8 (38.10)	1088 (55.14)	0.12
No	13 (61.90)	885 (44.86)	
Intrathecal chemotherapy			
Yes	3 (14.29)	921 (46.68)	0.003
No	18 (85.71)	1052 (53.32)	

Abbreviations: CPP, central precocious puberty; Gy, gray; HP, hypothalamic-pituitary; RT, radiation therapy; SJLIFE, St. Jude Lifetime Cohort Study

7

Declining free thyroxine levels over time in irradiated childhood brain tumor survivors

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Abstract

Objective

The incidence of cranial radiotherapy (cRT)–induced central hypothyroidism (TSHD) in childhood brain tumor survivors (CBTS) is reported to be low. However, TSHD may be more frequent than currently suspected, as its diagnosis is challenging due to broad reference ranges for free thyroxine (FT4) concentrations. TSHD is more likely to be present when FT4 levels progressively decline over time. Therefore, we determined the incidence and latency time of TSHD, and changes of FT4 levels over time in irradiated CBTS.

Design

Nationwide, 10-year retrospective study of irradiated CBTS.

Methods

TSHD was defined as "diagnosed" when FT4 concentrations were below the reference range with low, normal or mildly elevated thyrotropin levels, and as "presumed" when FT4 declined ≥ 20% within the reference range. Longitudinal FT4 concentrations over time were determined in growth hormone deficient (GHD) CBTS with and without diagnosed TSHD from cRT to last follow-up (paired *t*-test).

Results

Of 207 included CBTS, the 5-year cumulative incidence of diagnosed TSHD was 20.3%, which occurred in 50% (25/50) of CBTS with GHD by 3.4 years (range, 0.9–9.7) after cRT. Presumed TSHD was present in 20 additional CBTS. The median FT4 decline in GH-deficient CBTS was 41.3% ($P < 0.01$) to diagnosis of TSHD and 12.4% ($P = 0.02$) in GH-deficient CBTS without diagnosed TSHD.

Conclusions

FT4 concentrations in CBTS significantly decline over time after cRT, also in those not diagnosed with TSHD, suggesting that TSHD occurs more frequently and earlier than currently reported. The clinical relevance of cRT-induced FT4 decline over time should be investigated in future studies.

Introduction

Childhood brain tumor survivors (CBTS) have an increased risk of developing central hypothyroidism due to damage of the hypothalamic–pituitary (HP) region, especially after exposure to cranial radiotherapy (cRT).[1,2] The prevalence and latency times of cRT-induced HP dysfunction vary among patients, with growth hormone deficiency (GHD) usually occurring first and at a prevalence ranging from 29.0% to 39.1%.[3] In contrast, central hypothyroidism primarily occurs after high-dose cRT, with a prevalence ranging between 2.6% to 14.9%.[4]

Detection of central hypothyroidism may be challenging.[5] Its diagnosis is generally based on plasma free thyroxine (FT4) concentrations below those of the reference range, in combination with low, normal or mildly elevated thyrotropin (TSH) levels. However, the use of population-based FT4 reference ranges as diagnostic criteria for central hypothyroidism is questionable because the variability of FT4 concentrations within individuals is small, in contrast with large interindividual differences.[6,7] This suggests that an individual reduction in thyroid function within the reference range can be indicative of central hypothyroidism in CBTS who receive cRT. Previous studies have suggested that central hypothyroidism is underdiagnosed in patients with FT4 concentrations in the lower tertile of the reference range.[8,9]

Changes in FT4 concentration over time within one individual may be considered abnormal, even if they are maintained within the reference range.[6] For this reason, adults with ≥ 20% reductions in FT4 concentrations may be presumed to have mild central hypothyroidism and may be replaced with levothyroxine therapy (LT4), although high-quality evidence supporting this is lacking.[10] According to a recent guideline for surveillance of HP deficiencies (HPDs) in childhood cancer survivors, the diagnosis central hypothyroidism is more likely when FT4 concentrations are progressively declining over time.[4] A decline in FT4 concentrations, even those that remain within the lower tertile of the reference range, may thus be indicative of early damage to TSH-secreting cells due to radiation exposure. However, this has not been systematically assessed, and the clinical consequences of declining FT4 concentrations in these patients remain unclear. To this end, we retrospectively analyzed the incidence and latency time of "diagnosed" central hypothyroidism (i.e., FT4 concentrations below those of the reference range) and "presumed" central hypothyroidism (i.e., decline in FT4 concentration ≥ 20% with levels in the lower tertile of the reference range during follow-up) in a nationwide cohort of longitudinally assessed CBTS who received cRT. Secondly, we assessed the clinical effects of central hypothyroidism on height and weight outcomes during follow-up.

Subjects and methods

Patients

All patients were younger than 18 years at the time of diagnosis of a primary brain tumor, excluding craniopharyngioma or a pituitary gland tumor, between January 2002 and December 2012 (n = 258). The patients received cranial or craniospinal irradiation and had survived ≥ 2 years after diagnosis with either stable residual disease or no evidence of disease after completion of therapy at the time of follow-up. The methodology we used for patient selection has been described in detail.[11] Because both the pituitary and thyroid gland were exposed to radiotherapy during craniospinal irradiation, we limited the interference of thyroidal dysfunction on thyroid function parameters by excluding all patients with overt primary or subclinical (primary) hypothyroidism, as defined below (n = 39). In addition, patients with HPDs before receiving cRT were excluded (n = 12). Because the data were collected retrospectively, our institutional review board determined that the Act on Medical Research Involving Human Subjects did not apply to our study and provided a waiver for informed consent.

Definitions used for endocrine deficiencies

Central hypothyroidism

Diagnosed central hypothyroidism was defined as FT4 concentrations below those of each institutional age-specific reference range, in combination with low, normal or mildly elevated TSH concentrations (i.e. <7 mIU/L), or by the use of LT4 for documented diagnoses of central hypothyroidism. Presumed central hypothyroidism was defined as ≥ 20% decline in individual FT4 concentration that remained within the lower tertile of the age-specific reference intervals from the time of cRT to last follow-up, in combination with normal TSH concentrations.

Primary hypothyroidism

Overt primary hypothyroidism was defined as elevated plasma TSH concentrations (i.e. ≥7 mIU/L) in combination with low FT4 concentrations, according to those of each institutional age-specific reference range, or by LT4 administration for documented diagnoses of primary hypothyroidism. Subclinical primary hypothyroidism was defined as FT4 concentrations within those of each institutional age-specific reference range in combination with raised TSH levels at last follow-up.

Growth hormone deficiency

GHD was defined as insufficient peak responses after one or more GH stimulation tests (<20 mU/L) or a peak GH <30 mU/L in combination with an insulin-like growth factor-1 (IGF1) concentration <-2 standard deviation score (SDS). The date of GHD diagnosis was recorded as the date that the last GH stimulation test was performed to establish GHD diagnosis.

Adrenocorticotropic hormone deficiency

Adrenocorticotropic hormone deficiency (ACTHD) was defined by the use of hydrocortisone maintenance or substitution for suspected hypocortisolism, as documented by the treating endocrinologist at the last follow-up.

Luteinizing hormone and follicle-stimulating hormone deficiency

Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) deficiency (LH/FSHD) was defined by repeatedly low LH and/or FSH concentrations in the absence of pubertal development (girls aged >12 years, puberty stage B1; boys aged >13 years, testes volumes < 4 mL) or by use of estrogens or testosterone treatment for documented LH/FSHD cases at last follow-up.

Data collection

Data were retrospectively collected from patient medical records, which included demographic and tumor-related characteristics, treatment modalities, anthropometrics (i.e., height and weight) and use of antiepileptic drugs until the last follow-up for each patient. The cRT dose comprised the total cRT doses prescribed for tumor treatment. All endocrine laboratory measurements, including basal measurements of IGF1, FT4 and TSH, as well as dynamic testing results for GHD, were collected together with the age-specific reference ranges for FT4 and TSH concentrations of each institution. The lower limits of the FT4 reference ranges varied between 8 and 12.5 pmol/L, and the upper limits ranged from 18 to 26 pmol/L. The lower tertiles of each institutional-specific reference ranges were defined by dividing the difference between the upper and lower limits by three. The lower limits of the TSH assays were between 0.3 and 0.5 mIU/L, whereas the highest reported upper limit was 5.0 mIU/L.

Statistical analyses

Descriptive analyses were performed for the prevalence and cumulative incidence of HPDs in all CBTS who received cRT. For diagnosed central hypothyroidism, presumed central hypothyroidism, and GHD, the latency time was also examined. Because we assumed that GHD has the shortest latency time after cRT treatment, the presence or absence of GHD during follow-up was used to categorize the cohort into distinct subgroups. The first subgroup consisted of CBTS who experienced GHD during follow-up. Changes in FT4 concentration (absolute and percent changes in FT4 (ΔFT4)) were compared at the following time points with paired analyses: (1) at the time of cRT start, (2) at diagnosis of GHD, (3) after starting GH treatment and (4) at diagnosis of central hypothyroidism or at the last follow-up if central hypothyroidism was not diagnosed. A second subgroup consisted of all CBTS who received cRT but did not receive diagnoses of GHD or other HPDs at follow-up. Changes in FT4 concentration (absolute and ΔFT4) were compared at the time of cRT start and at the last follow-up. Missing values are indicated in the figures and explained in the legends.

Between-group differences were examined by Student *t*-tests for continuous data with normal distributions and X^2 or Fisher exact tests for categorical data. Non-normally distributed data were analyzed by Mann–Whitney *U* tests. Cumulative incidence was calculated by using the Kaplan-Meier survival method (1 minus Kaplan–Meier probability). Paired *t*-tests were used to evaluate differences in ΔFT4 concentrations within groups, and Wilcoxon signed-rank tests were used for TSH concentrations. Serial FT4 and TSH measurements for each individual were obtained from the same clinical laboratories to allow proper paired analyses. A *P* value less than 0.05 was considered statistically significant. Analyses were performed with SPSS 21.0 for Windows (IBM SPSS System Inc). GraphPad Prism 7.02 was used to generate figures for longitudinal data.

Results

Study cohort

We included a total of 207 CBTS who received cRT in our study (Figure 1, Table 1). The median follow-up time after brain tumor diagnosis was 6.9 years (range, 2.0–13.3) and 6.1 years (range, 0.2–12.7) after cRT start. The median cRT dose was 54 Gy (range, 12.5–72.0).

Table 1. Demographic and treatment characteristics of the study cohort (n = 207)

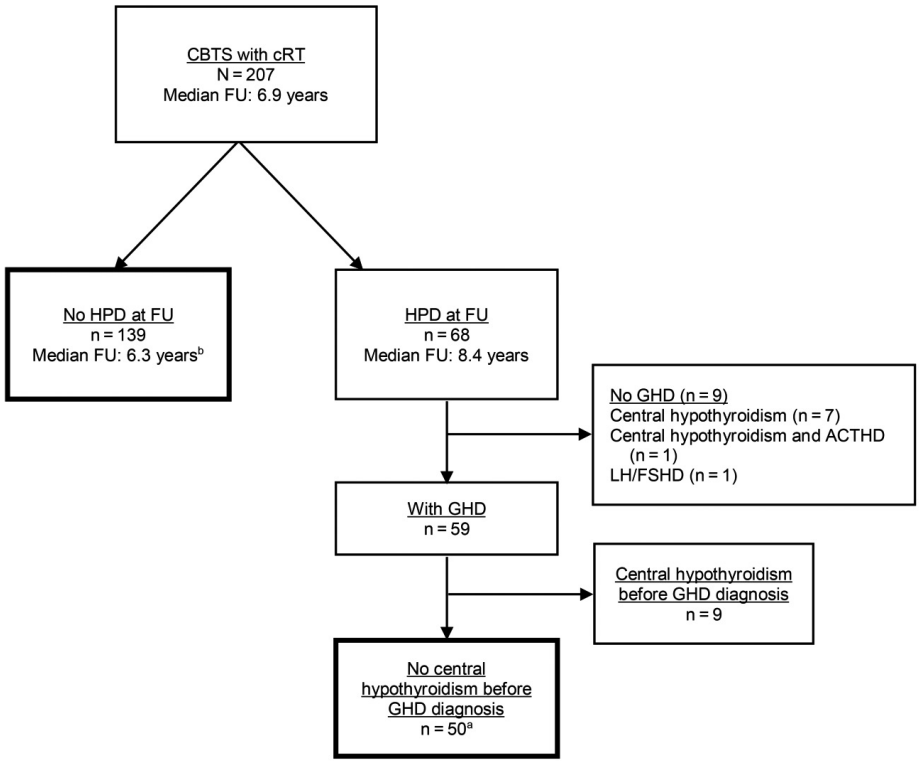
Characteristic	No.	%
Sex		
Male	125	60.4
Female	82	39.6
Age at diagnosis brain tumor (years)		
Median (range)	8.9 (0.1–17.7)	
Age at follow-up (years)		
Median (range)	16.2 (4.7–27.4)	
Follow-up time after brain tumor diagnosis (years)		
Median (range)	6.9 (2.0-13.3)	
Follow-up time after cRT (years)		
Median (range)	6.1 (0.2–12.7)	
Histology		
Medulloblastoma	63	30.4
Low-grade glioma	45	21.7
High-grade glioma	13	6.3
sPNET	7	3.4
Ependymoma	43	20.8
Choroid plexus tumor	1	0.5

Table 1. Continued

Characteristic	No.	%
Germ-cell tumor	15	7.2
ATRT	5	2.4
Other [a]	8	3.9
Without histology	7	3.4
Location of primary tumor		
Infratentorial region	107	51.7
Supratentorial region	80	38.6
Suprasellar region	20	9.7
Hydrocephalus at diagnosis [b]		
Yes	142	68.6
No	65	31.4
Single and combined treatment modalities applied at any time		
cRT only	5	2.4
Neurosurgery + cRT	84	40.6
cRT + CT	2	1.0
Neurosurgery + cRT + CT	116	56.0
cRT localization		
Cranial	132	63.8
Craniospinal	75	36.2
Age at primary cRT (years)		
Median (range)	9.7 (1.5–22.9)	
< 5	41	19.8
5–10	67	32.4
> 10	99	47.8
Total cRT dose (Gy)		
Median (range)	54.0 (12.5–72.0)	
Recurrence/progression requiring treatment		
Yes	63	30.4
No	144	69.6

[a] Includes meningioma (n = 4), schwannoma (n = 3), and desmoplastic small-round-cell tumor (n= 1)
[b] Hydrocephalus was defined as the presence of increased ventricle width during magnetic resonance imaging
Abbreviations: ATRT, atypical teratoid rhabdoid tumor; CT, chemotherapy; cRT, cranial radiotherapy; sPNET: supratentorial primitive neuro-ectodermal tumor

Figure 1. Flow chart of retrospective study cohort



Abbreviations: ACTHD, adrenocorticotropic hormone deficiency; CBTS, childhood brain tumor survivors; cRT, cranial radiotherapy; FT4, free thyroxine; FU, follow-up time after diagnosis; GHD, growth hormone deficiency; HPD, hypothalamic–pituitary deficiency; LH/FSHD: luteinizing hormone–follicle-stimulating hormone deficiency.

[a] FT4 concentrations were longitudinally analyzed in this cohort at cRT start, at GHD diagnosis, after GH treatment, at central hypothyroidism diagnosis, or at last follow-up without central hypothyroidism diagnosis.

[b] FT4 concentrations were longitudinally analyzed at cRT start and at last-follow-up in this cohort.

Incidence of anterior pituitary deficiencies

Sixty-eight of 207 (32.9%) CBTS experienced one or more HPDs after exposure to cRT. Thirty-three of these (48.5%) experienced one HPD, and 35 (51.5%) experienced multiple HPDs at last follow-up. The 5-year cumulative incidence was 31.4% (95% confidence interval (CI) 21.8–41.4) for GHD, 20.3% (95% CI 10.7–32.1) for central hypothyroidism, 6.6% (95% CI 0.7–22.6) for ACTHD, and 3.1% (95% CI 0.02–23.9) for LH/FSHD. The latency time of GHD and central hypothyroidism after cRT start was 2.5 years (range, 0.6–7.4) and 2.7 years (range, 0.3–9.7), respectively. The prevalence of HPDs at last-follow-up was 28.5% (59/207) for GHD, 20.3%

(42/207) for central hypothyroidism, 6.3% (13/207) for ACTHD and 4.3% (9/207) for LH/FSHD. Figure 2 summarizes the prevalence and overlap of all HPDs. The prevalence of antiepileptic drug use was similar among CBTS with and without diagnosed central hypothyroidism (17.6 vs 11.5%, *P = 0.55*).

Nine of the 68 CBTS (13.2%) experienced an HPD other than GHD (i.e., central hypothyroidism, ACTHD, LH/FSHD, or a combination of these). In two of these nine CBTS, GH stimulation tests were performed, ruling out GHD. In two other CBTS, low IGF1 concentrations were found, suggestive of GHD. In the 59 CBTS with GHD, nine (15.3%) had central hypothyroidism before GHD diagnosis. In these CBTS, IGF1 concentrations at diagnosis of central hypothyroidism were low (median IGF1 SDS, –2.57; range, –5.11 to –1.79).

Longitudinal effect of cranial radiotherapy on free thyroxine concentrations

CBTS with GHD

We performed paired analyses of the longitudinal FT4 concentrations in 50 CBTS who did not have central hypothyroidism before GHD. Their median FT4 concentrations declined by 9.0% (–1.4 pmol/L) from cRT start to GHD diagnosis ($P < 0.01$) after a median follow-up period of 1.7 years (Figure 3). In the 45 CBTS who subsequently received GH treatment, a 14.9% (–2.0 pmol/L) decline in FT4 occurred after a median period of 0.6 years ($P < 0.01$). The total median decline of FT4 was 26.1% (–3.5 pmol/L) between start cRT and after GH treatment ($P < 0.01$). TSH concentrations did not significantly change over time (median TSH at GHD diagnosis, 2.7 mIU/L vs median TSH at GH treatment start, 2.8 mIU/L; $P = 0.44$)

In 25 of the 50 CBTS with GHD, central hypothyroidism was diagnosed 3.4 years (range, 0.9–9.7) after cRT start and 0.7 years (range, 0.1–5.9) after GHD diagnosis. The median FT4 decline in these CBTS was 41.3% (–6.1 pmol/L) from cRT start to central hypothyroidism diagnosis (Figure 4A) ($P < 0.01$). In these CBTS, central hypothyroidism may have been already presumed 2.4 years after cRT start. In the 25 CBTS with GHD who did not have diagnosed central hypothyroidism, the median decline in FT4 concentration was 12.4% (–2.1 pmol/L) from cRT start to last follow-up ($P = 0.02$). In five of these 25 CBTS, presumed central hypothyroidism was present. CBTS with diagnosed central hypothyroidism were most often medulloblastoma survivors and were older at diagnosis, cRT start and follow-up than were CBTS without central hypothyroidism. The characteristics of the 50 CBTS with GHD and with or without diagnosed central hypothyroidism are listed in Table 2.

Figure 2. Prevalence and overlap of hypothalamic-pituitary deficiencies in childhood brain tumor survivors who received cranial irradiation

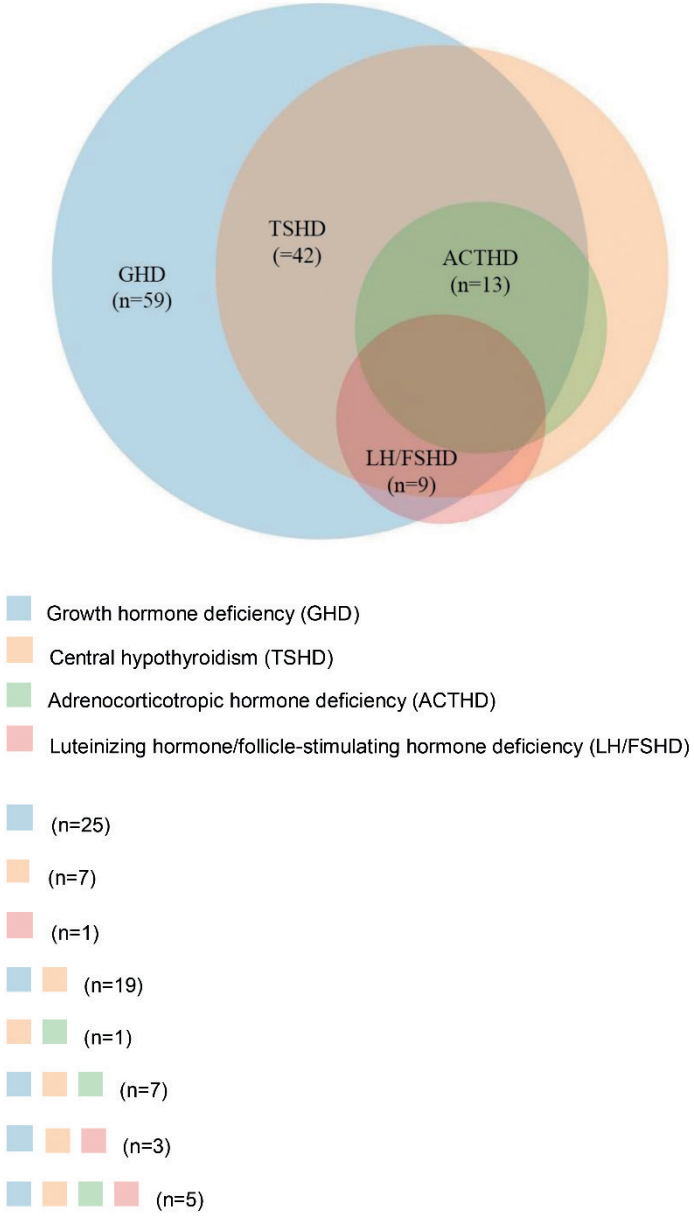
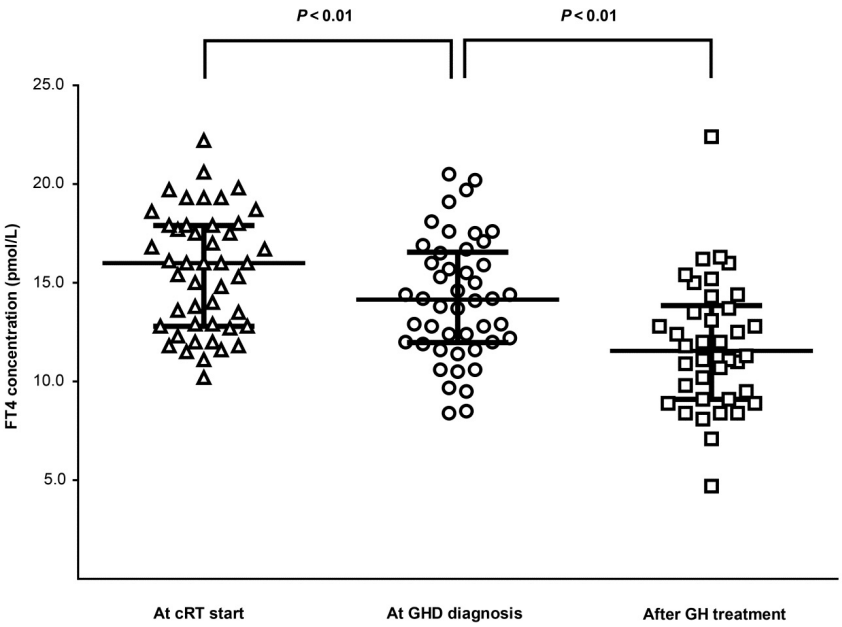


Figure 3. Scatter dot plot (median with interquartile range) of absolute FT4 concentrations at cRT start, before GHD diagnosis, and after GH treatment start



Available FT4 concentrations for 50 CBTS with GHD were compared. FT4 concentrations before cRT start could be retrieved for 24 CBTS. In the remaining 26 CBTS, the first measured FT4 concentration after cRT start was deemed the baseline value for cRT start. FT4 concentrations could be compared at cRT start and at GHD diagnosis for 46 CBTS. FT4 concentrations could be compared at GHD diagnosis and after GH treatment for 38 CBTS. Median FT4 concentrations declined from cRT start to GHD diagnosis ($P < 0.01$; 95%CI 0.82–2.14; paired *t*-test, n = 46) and after GH treatment ($P < 0.01$; 95%CI 1.06–3.33; paired *t*-test, n = 38). Abbreviations: CBTS, childhood brain tumor survivors; cRT, cranial radiotherapy; FT4, free thyroxine; GH, growth hormone; GHD, growth hormone deficiency

Table 2. Demographic and treatment characteristics of growth hormone deficient CBTS, with and without subsequent central hypothyroidism

	No diagnosed central hypothyroidism after GHD (n = 25)		Diagnosed central hypothyroidism after GHD (n = 25)		
Characteristic	**No.**	**%**	**No.**	**%**	***P***
Sex					0.76
Male	17/25	68.0	18/25	72.0	
Female	8/25	32.0	7/25	28.0	
Age at diagnosis brain tumor (years)					< 0.01 [b]

Table 2. Continued

Characteristic	No diagnosed central hypothyroidism after GHD (n = 25) No.	%	Diagnosed central hypothyroidism after GHD (n = 25) No.	%	*P*
Median (range)	4.4 (0.6–12.3)		9.3 (2.4–13.1)		
Age at follow-up (years)					< 0.01 [b]
Median (range)	12.6 (5.1–23.1)		16.9 (9.8–25.0)		
Follow-up time after brain tumor diagnosis (years)					0.19
Median (range)	8.2 (2.5–13.3)		8.9 (3.3–12.4)		
Histology					< 0.01 [b]
Medulloblastoma	15/25	60.0	20/25	80.0	
Low-grade glioma	1/25	4.0	5/25	20.0	
sPNET	1/25	4.0	–	–	
Ependymoma	5/25	20.0	–	–	
ATRT	1/25	4.0	–	–	
Meningioma	1/25	4.0	–	–	
Without histology	1/25	4.0	–	–	
Location of primary tumor					1.00
Infratentorial region	21/25	84.0	21/25	84.0	
Supratentorial region	1/25	4.0	–	–	
Suprasellar region	3/25	12.0	4/25	16.0	
Hydrocephalus at diagnosis [a]					0.51
Yes	20/25	80.0	18/25	72.0	
No	5/25	20.0	7/25	28.0	
Single and combined treatment modalities applied at any time					0.67
Neurosurgery + cRT	3/25	12.0	2/25	8.0	
cRT + CT	1/25	4.0	–	–	
Neurosurgery + cRT + CT	21/25	84.0	23/25	92.0	
cRT localization					0.05
Cranial	9/25	36.0	3/25	12.0	
Craniospinal	16/25	64.0	22/25	88.0	
Age at primary cRT (years)					< 0.01 [b]
Median (range)	5.1 (1.8–12.4)		9.9 (3.0–15.6)		
< 5	11/25	44.0	2/25	8.0	
5–10	9/25	36.0	11/25	44.0	
> 10	5/25	20.0	12/25	48.0	
Total cRT dose (Gy)					0.72

Table 2. Continued

Characteristic	No diagnosed central hypothyroidism after GHD (n = 25) No.	%	Diagnosed central hypothyroidism after GHD (n = 25) No.	%	*P*
Median (range)	54.0 (15.0–68.0)		54.0 (45.0–72.0)		
Recurrence/progression requiring treatment					0.33
Yes	8/25	32.0	5/25	20.0	
No	17/25	68.0	20/25	80.0	

[a] Hydrocephalus was defined as the presence of increased ventricle width during magnetic resonance imaging
[b] Significant *P* values
Abbreviations: ATRT, atypical teratoid rhabdoid tumor; CT, chemotherapy; CBTS, childhood brain tumor survivors; cRT, cranial radiotherapy; sPNET: supratentorial primitive neuro-ectodermal tumor

CBTS without growth hormone or other hypothalamic–pituitary deficiencies

Of the CBTS who received cRT but did not have HPDs during follow-up (n = 139), the median ΔFT4 was –4.4% (–0.7 pmol/L) from cRT start to last follow-up ($P = 0.02$) after a median time of 4.2 years (range, 0.2–11.3). Presumed central hypothyroidism was present in 15 of these CBTS (Figure 4B).

Clinical effects on height and weight

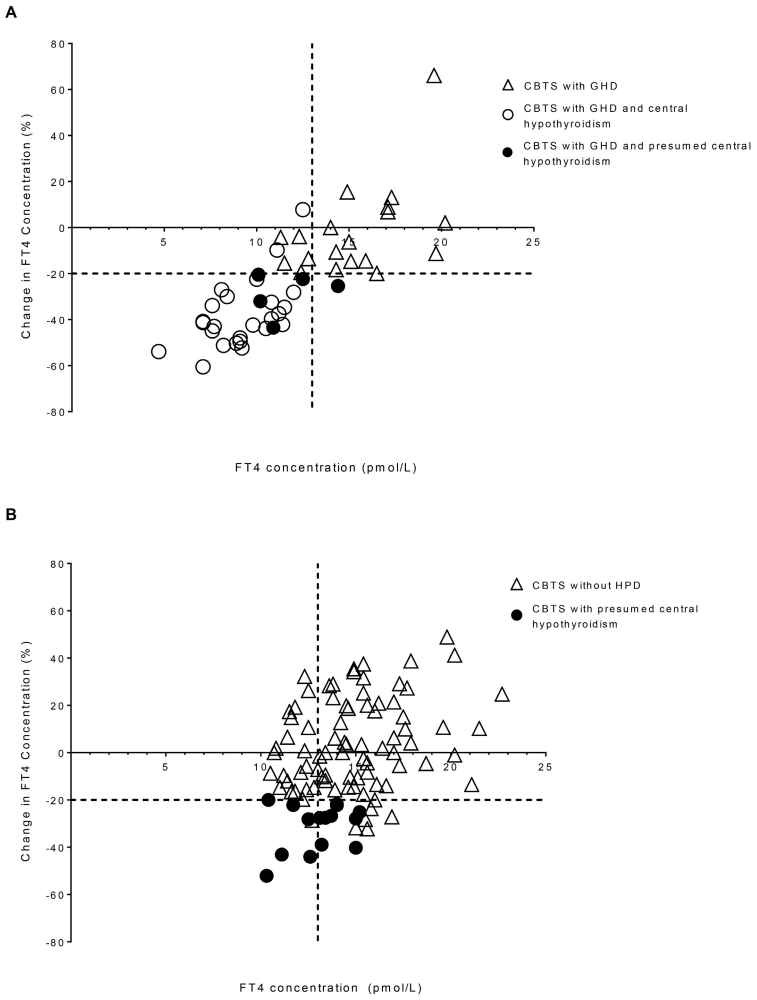
All CBTS who received cRT but did not have GHD were included for analysis of height and weight (n = 148). Neither height or BMI SDSs of patients with presumed and diagnosed central hypothyroidism were significantly different from those of patients without central hypothyroidism.

Discussion

We performed a large-cohort study of CBTS who received cRT and found a high incidence of diagnosed central hypothyroidism. More importantly, our longitudinal analyses revealed marked declines in FT4 concentrations over time, with a decline of even >40% from initial FT4 values before the diagnosis of central hypothyroidism was made. In addition, a decline in FT4 concentration ≥20% (i.e. presumed central hypothyroidism) was present in 20 additional CBTS.

Central hypothyroidism in CBTS has been reported to be infrequent or absent after low-dose cRT.[12-17] The relatively high (20.3%) 5-year cumulative incidence of central hypothyroidism in our cohort may be due to the high-dose cRT that these patients received, as the vulnerability of the HP–thyroid axis is highly dose dependent.[18,19] Our observations are concordant with the 4-year cumulative incidence (23%) reported in a large cohort study including CBTS who received cRT doses ≥ 40 Gy.[20]

Figure 4. Scatter dot plot of the percent change in FT4 concentration (ΔFT4), in relation to absolute FT4 concentrations of all CBTS with GHD and without GHD or other HPDs who received cRT. (A) CBTS with GHD (n = 50) and (B) CBTS without GHD or other HPDs (n = 139)



(A) ΔFT4 was calculated by comparing FT4 concentrations at cRT start to central hypothyroidism diagnosis or to last follow-up if central hypothyroidism was not diagnosed. Central hypothyroidism was presumed when FT4 levels declined ≥20% and were in the lower tertile of the reference range (n = 5). (B) ΔFT4 was calculated by comparing FT4 concentrations at cRT start to last follow-up. FT4 concentrations before cRT start could be retrieved for 64 CBTS. The first measured FT4 concentration after the cRT start was deemed the baseline FT4 value at cRT start for the remaining 75 CBTS. FT4 concentrations could be compared between baseline and last follow-up for 98 CBTS. Central hypothyroidism was presumed when FT4 declined ≥20% and was in the lower tertile of the reference range (n = 15). Dashed lines indicate ΔFT4 of –20%.
Abbreviations: CBTS, childhood brain tumor survivors; cRT, cranial radiotherapy; FT4, free thyroxine; GHD, growth hormone deficiency; HPD, hypothalamic–pituitary deficiency

We demonstrated a clear decline in FT4 concentrations over time that occurred simultaneously with or preceded GHD diagnosis. In previous studies, a decline in total T4 concentrations after cRT by 1.5% per year has been reported.[13] However, in one study only children who received low-dose cRT were included (15–24 Gy), and only single FT4 concentrations from different CBTS were correlated with follow-up time. In another study, the same cross-sectional analysis was applied to a cohort of CBTS receiving high-dose cRT (53.6 Gy), and an inverse association between serum FT4 concentrations and follow-up times was reported.[21]

The usefulness of the population-based FT4 reference ranges used to establish central hypothyroidism diagnoses is debatable.[22] Diagnostic tests, such as dynamic TRH testing or the use of the nocturnal TSH rise have been suggested as alternative markers of central hypothyroidism.[8] However, dynamic testing of the HP–thyroid axis requires hospital admission, limiting its use as a screening tool. In addition, possible abnormalities of TSH dynamics upon dynamic testing may represent subtle variations and may not be indicative for central hypothyroidism.[23] Because intraindividual differences in FT4 concentrations in healthy subjects are small [24], some guidelines recommend treatment with LT4 when ≥ 20% declines in FT4 concentrations are observed.[10] Following these guidelines, our findings suggest that treatment could have been provided 1 year earlier in CBTS with diagnosed central hypothyroidism and might have been started in an additional 20 CBTS with presumed central hypothyroidism.

Several factors may affect FT4 concentrations. In general, FT4 concentrations decrease with age, especially when entering puberty.[25] This may partially explain why the CBTS in our study with diagnosed central hypothyroidism were older than those without diagnosed central hypothyroidism. However, the follow-up time of our cohort (6.9 years) was too short to support a large interference of age with the observed declining FT4 concentrations. Moreover, the follow-up times of CBTS with GHD and with and without diagnosed central hypothyroidism were similar, suggesting that age and not follow-up time unmasked the presence of central hypothyroidism in our cohort. Nutritional status, BMI and antiepileptic drug use are also factors that may affect thyroid function parameters. In our cohort, we did not observe significant changes in BMI over time and the prevalence of antiepileptic drug use was similar among CBTS with and without diagnosed central hypothyroidism. However, start and stop dates of antiepileptic drug use had not been retrieved from medical charts. In addition, information regarding other drugs that potentially influenced thyroid function parameters was not collected. This limits our ability to draw strong conclusions about potential interference of (antiepileptic) drug use and thyroid function parameters. Finally, initiation of GH treatment may induce changes in FT4 and TSH concentrations, possibly by increased T4 to T3 conversion and inhibition of TSH secretion.[26] Although these changes are often transient in non-GH-deficient individuals, in patients with

organic GH deficiency or multiple pituitary hormone deficiencies, alterations in thyroid function parameters seem more pronounced and result in the unmasking of central hypothyroidism.[27]

The clinical significance of mild (i.e., presumed) central hypothyroidism is an issue of debate. Growth acceleration in children who receive GH therapy occurs only after LT4 treatment in cases of concomitant central hypothyroidism.[28] Another study reported that reduced patient heights were found at start of GH treatment in children with multiple pituitary hormone deficiencies, as compared to the heights of children with true isolated GHD.[29] These findings suggest that when unrecognized central hypothyroidism is present in children with GHD, it may have already affected linear growth. We did not find any adverse effects on height or BMI from declining FT4 concentrations in our cohort. However, these clinical parameters were not systematically assessed, and a large proportion of CBTS had not yet reached adult height. Therefore, definite conclusions regarding the clinical consequences of declining FT4 concentrations cannot be drawn and should be assessed in future studies. Patients who experience central hypothyroidism after GH therapy start have a lower quality of life than do patients who remain euthyroid. This difference in quality of life is reversible, as it was shown to resolve after LT4 treatment in adults with hypothyroidism.[9] Central hypothyroidism may decrease left ventricular ejection fraction in patients with pituitary disease, even when FT4 concentrations remain within the lower range of the reference interval.[30] CBTS may have an altered metabolic state, increasing their risk for dyslipidemia and heart disease because of previous exposures to chemotherapy (e.g., alkylating agents), impaired neurologic function, reduced physical activity, and comorbid endocrine deficiencies. Suboptimal thyroid hormone concentrations may further negatively influence the metabolic state. These arguments may be used to advocate timely and adequate supplementation of LT4 in CBTS with a history of cRT aiming to restore FT4 concentrations to the highest third of the reference range to encourage linear growth potential and improve quality of life, metabolic state and cardiac health. The potential benefits of treatment, however, should be considered in the context of the possible negative aspects of overdiagnosis, overtreatment, daily medication administration and frequent blood tests. Prospective studies with systematic screening for central hypothyroidism are required to define the exact prevalence, most optimal diagnostic criteria, and subsequent clinical relevance of mild central hypothyroidism in CBTS.

The comprehensive nature and the intraindividual analyses of FT4 concentrations over time exemplify the strengths of our study. In addition, we evaluated thyroid function parameters only after completion of therapy, excluding FT4 declines from nonthyroidal illnesses or the effects of supportive care drugs such as dexamethasone on thyroid function determinants.[31] Nevertheless, the retrospective design, lack of screening guidelines for HPDs in CBTS, and nonsystematic reporting of HP–thyroid function parameters, resulting in missing values for a proportion of CBTS, are limitations of our study. In addition, the lack of systematic and repetitive screening

may have underestimated the true prevalence of HPDs in our cohort, given the time dependent character of cRT-induced HPDs. Especially the occurrence of ACTHD might have been underrepresented in our cohort, as dynamic testing was only performed in a minority of all CBTS. Moreover, we defined baseline FT4 concentrations for individual CBTS as FT4 concentrations at cRT start. However, this may underestimate actual FT4 baseline concentrations, as illnesses before cRT were not considered. This may account for our observation of increased FT4 concentrations during follow-ups in a substantial number of CBTS. However, this also suggests that the actual FT4 declines in CBTS with presumed central hypothyroidism may have been even larger. A possible coexistence of thyroid-initiated hypothyroidism (leading to combined or mixed hypothyroidism) after craniospinal radiotherapy should be considered because both the HP and thyroid glands are included in the radiation field. We were not able to ascertain detailed cRT dose information for the pituitary or thyroid gland. Therefore, no conclusion can be drawn upon the risk for central hypothyroidism in relation to radiation dose. Also, the HP region of the GH-deficient and nonGH-deficient groups may have been exposed to different cRT doses, which may have biased the comparison results between both groups. In addition, other tumor and treatment characteristics, such as tumor involvement in the HP region, should be considered as cause for the occurrence of central hypothyroidism at follow-up. Secondly, in patients exposed to craniospinal irradiation, it can be difficult to make a clear distinction between primary and central hypothyroidism, and combined forms of hypothyroidism may be present. Declines in FT4 concentration may have been exacerbated by radiation damage to the thyroid gland. For this reason we have used stringent diagnostic criteria for central hypothyroidism. In addition, the large proportion of CBTS with known GHD included in our analysis suggests that these patients may have already experienced cRT-induced HP damage.

In conclusion, FT4 concentrations of irradiated CBTS significantly decline over time, suggesting that high-dose cRT causes more frequent and earlier damage to TSH- or T4-secreting cells than is currently reported. Future prospective studies are required to confirm our findings and the clinical relevance of cRT-induced FT4 decline in CBTS.

References

1. Tonorezos ES, Hudson MM, Edgar AB, et al. Screening and management of adverse endocrine outcomes in adult survivors of childhood and adolescent cancer. *Lancet Diabetes Endocrinol.* 2015;3(7):545-555.
2. Crowne E, Gleeson H, Benghiat H, Sanghera P, Toogood A. Effect of cancer treatment on hypothalamic-pituitary function. *Lancet Diabetes Endocrinol.* 2015;3(7):568-576.
3. Mulder RL, Kremer LC, van Santen HM, et al. Prevalence and risk factors of radiation-induced growth hormone deficiency in childhood cancer survivors: a systematic review. *Cancer Treat Rev.* 2009;35(7):616-632.
4. Sklar CA, Antal Z, Chemaitilly W, et al. Hypothalamic-Pituitary and Growth Disorders in Survivors of Childhood Cancer: An Endocrine Society Clinical Practice Guideline. *The Journal of clinical endocrinology and metabolism*. 2018.
5. Beck-Peccoz P, Rodari G, Giavoli C, Lania A. Central hypothyroidism - a neglected thyroid disorder. *Nat Rev Endocrinol.* 2017.
6. Alexopoulou O, Beguin C, De Nayer P, Maiter D. Clinical and hormonal characteristics of central hypothyroidism at diagnosis and during follow-up in adult patients. *Eur J Endocrinol.* 2004;150(1):1-8.
7. Westgard QC. Desirable specifications for total error, imprecision, and bias, derived from intra- and inter-individual biologic variation. Accessed 22 February 2018. Madison, WI, USA: Westgard QC. (available at: https://www.westgard.com/biodatabase1.htm).
8. Rose SR, Lustig RH, Pitukcheewanont P, et al. Diagnosis of hidden central hypothyroidism in survivors of childhood cancer. *J Clin Endocrinol Metab.* 1999;84(12):4472-4479.
9. Agha A, Walker D, Perry L, et al. Unmasking of central hypothyroidism following growth hormone replacement in adult hypopituitary patients. *Clinical Endocrinology.* 2007;66(1):72-77.
10. Fleseriu M, Hashim IA, Karavitaki N, et al. Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2016;101(11):3888-3921.
11. Clement SC, Schouten-van Meeteren AY, Boot AM, et al. Prevalence and Risk Factors of Early Endocrine Disorders in Childhood Brain Tumor Survivors: A Nationwide, Multicenter Study. *J Clin Oncol.* 2016;34(36):4362-4370.
12. Follin C, Link K, Wiebe T, Moell C, Bjork J, Erfurth EM. Prolactin insufficiency but normal thyroid hormone levels after cranial radiotherapy in long-term survivors of childhood leukaemia. *Clinical endocrinology.* 2013;79(1):71-78.
13. Lando A, Holm K, Nysom K, et al. Thyroid function in survivors of childhood acute lymphoblastic leukaemia: the significance of prophylactic cranial irradiation. *Clin Endocrinol (Oxf).* 2001;55(1):21-25.
14. Livesey EA, Hindmarsh PC, Brook CG, et al. Endocrine disorders following treatment of childhood brain tumours. *Br J Cancer.* 1990;61(4):622-625.
15. Schmiegelow M, Feldt-Rasmussen U, Rasmussen AK, Poulsen HS, Muller J. A population-based study of thyroid function after radiotherapy and chemotherapy for a childhood brain tumor. *J Clin Endocrinol Metab.* 2003;88(1):136-140.
16. Oberfield SE, Allen JC, Pollack J, New MI, Levine LS. Long-term endocrine sequelae after treatment of medulloblastoma: prospective study of growth and thyroid function. *J Pediatr.* 1986;108(2):219-223.
17. Livesey EA, Brook CG. Thyroid dysfunction after radiotherapy and chemotherapy of brain tumours. *Arch Dis Child.* 1989;64(4):593-595.
18. Robinson IC, Fairhall KM, Hendry JH, Shalet SM. Differential radiosensitivity of hypothalamo-pituitary function in the young adult rat. *The Journal of endocrinology.* 2001;169(3):519-526.
19. Littley MD, Shalet SM, Beardwell CG, Robinson EL, Sutton ML. Radiation-induced hypopituitarism is dose-dependent. *Clin Endocrinol (Oxf).* 1989;31(3):363-373.

20. Laughton SJ, Merchant TE, Sklar CA, et al. Endocrine outcomes for children with embryonal brain tumors after risk-adapted craniospinal and conformal primary-site irradiation and high-dose chemotherapy with stem-cell rescue on the SJMB-96 trial. *J Clin Oncol.* 2008;26(7):1112-1118.

21. Constine LS, Woolf PD, Cann D, et al. Hypothalamic-pituitary dysfunction after radiation for brain tumors. *N Engl J Med.* 1993;328(2):87-94.

22. Persani L. Clinical review: Central hypothyroidism: pathogenic, diagnostic, and therapeutic challenges. *J Clin Endocrinol Metab.* 2012;97(9):3068-3078.

23. Darzy KH, Shalet SM. Circadian and stimulated thyrotropin secretion in cranially irradiated adult cancer survivors. *J Clin Endocrinol Metab.* 2005;90(12):6490-6497.

24. Andersen S, Pedersen KM, Bruun NH, Laurberg P. Narrow individual variations in serum T(4) and T(3) in normal subjects: a clue to the understanding of subclinical thyroid disease. *J Clin Endocrinol Metab.* 2002;87(3):1068-1072.

25. Lem AJ, de Rijke YB, van Toor H, de Ridder MA, Visser TJ, Hokken-Koelega AC. Serum thyroid hormone levels in healthy children from birth to adulthood and in short children born small for gestational age. *The Journal of clinical endocrinology and metabolism.* 2012;97(9):3170-3178.

26. Behan LA, Monson JP, Agha A. The interaction between growth hormone and the thyroid axis in hypopituitary patients. *Clinical endocrinology.* 2011;74(3):281-288.

27. van Iersel L, van Santen HM, Zandwijken GRJ, Zwaveling-Soonawala N, Hokken-Koelega ACS, van Trotsenburg ASP. Low FT4 Concentrations around the Start of Recombinant Human Growth Hormone Treatment: Predictor of Congenital Structural Hypothalamic-Pituitary Abnormalities? *Horm Res Paediatr.* 2018;89(2):98-107.

28. Sato T, Suzukui Y, Taketani T, Ishiguro K, Masuyama T. Enhanced peripheral conversion of thyroxine to triiodothyronine during hGH therapy in GH deficient children. *The Journal of clinical endocrinology and metabolism.* 1977;45(2):324-329.

29. Child CJ, Blum WF, Deal C, et al. Development of additional pituitary hormone deficiencies in pediatric patients originally diagnosed with isolated growth hormone deficiency due to organic causes. *European journal of endocrinology.* 2016;174(5):669-679.

30. Doin FC, Rosa-Borges M, Martins MR, Moises VA, Abucham J. Diagnosis of subclinical central hypothyroidism in patients with hypothalamic-pituitary disease by Doppler echocardiography. *European journal of endocrinology.* 2012;166(4):631-640.

31. van Santen HM, Thonissen NM, de Kraker J, Vulsma T. Changes in thyroid hormone state in children receiving chemotherapy. *Clinical endocrinology.* 2005;62(2):250-257.

8

Clinical significance of variation in free thyroxine concentrations after radiation therapy for pediatric brain tumors: a longitudinal study

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Submitted

Abstract

Context

Clinical significance of variation in free thyroxine (FT4) concentrations across the reference range in children given cranial radiation therapy (RT) is uncertain.

Objectives

To study longitudinal trends in FT4 in children receiving RT for brain tumors and risk factors and health outcomes associated with plasma FT4 concentrations.

Design and setting

Longitudinal, single-center cohort study.

Patients

Low-grade glioma or ependymoma patients (n=267; age≤25 years) who received RT (50.4–59.4 Gy) at a single institution (1996–2016) and underwent serial FT4 measurements.

Main Outcome Measure

A linear mixed-effects model with random intercept was used to investigate risk factors for longitudinal changes in FT4 concentrations. A 2-stage mixed-effects model was adopted to examine associations between clinical outcomes and plasma FT4 concentrations.

Results

FT4 concentrations significantly declined over time after RT (P<0.001). Females (P<0.001) and individuals given RT at a younger age (P<0.001) demonstrated greater declines in FT4 concentrations over time. The rate of weight gain, but not of height loss, increased with a higher FT4 decline rate (P< 0.001). Patients with lower baseline FT4 concentrations had increased risk of glucose disorder (OR=19.73, P=0.002) or dyslipidemia (OR=19.40, P=0.003) but not high fat mass (P=0.18) at last follow-up. Lower baseline FT4 concentrations were not associated with impaired scores for intelligence, attention, memory, or psychosocial functioning.

Conclusions

FT4 concentrations significantly decline in children receiving RT for brain tumors. Variation and trends in FT4 concentration after RT are associated with physical health outcomes. Future studies should assess whether continuous FT4 concentrations and trends, rather than population-based cut-off values, can better distinguish between euthyroid and hypothyroid states.

Introduction

Children with brain tumors exposed to radiation therapy (RT) have an increased risk of developing hypothalamic–pituitary (HP) disorders, including central hypothyroidism.[1-4] The prevalence of central hypothyroidism in childhood cancer survivors with central nervous system tumors or treated with RT, varies from 2.6% to 14.9% due to different diagnostic criteria used in studies.[5]

Data from non-cancer populations have raised concerns about potential associations between central hypothyroidism and adverse metabolic, cardiovascular, and neurocognitive health outcomes.[6-9] Children with brain tumors have high physical and neurocognitive morbidity, and central hypothyroidism may contribute to these adverse outcomes.

The diagnosis of central hypothyroidism is usually based on free thyroxine (FT4) concentrations below the reference range, with low, normal, or mildly elevated thyroid- stimulating hormone (TSH) concentrations. Consensus guidelines recommend the replacement of thyroxine therapy (levothyroxine [LT4]) primarily in individuals with FT4 concentrations below the normal range.[5,10,11] However, patients exposed to RT may have a decline in FT4 concentrations without crossing lower limits of the reference range during surveillance for central hypothyroidism.[12] In addition, emerging cross-sectional data demonstrate that variations in thyroid function within the reference range can negatively affect health outcomes.[13] Thus, well-designed longitudinal studies are required to determine the clinical significance of variations and trends in FT4 concentrations in irradiated pediatric patients with brain tumors. Optimizing the timing of hormone replacement therapy might improve health-related outcomes in this vulnerable population.

Thus, the aims of this study were to (1) describe longitudinal trends of FT4 concentrations in a large population of systematically followed children and adolescents diagnosed with a brain tumor and exposed to high-dose RT; (2) examine effects of sociodemographic and treatment characteristics on longitudinal trends of FT4 concentrations; and (3) assess associations between variations in plasma FT4 concentrations and adverse physical and neurocognitive outcomes.

Methods

Patients

This retrospective longitudinal study included patients diagnosed with intracranial ependymoma or low-grade glioma (LGG) irradiated before the age of 25 years and treated with conformal or intensity-modulated RT using photons between 1996 and 2016. The prescribed RT dose to the primary site was 50.4–54 Gy for LGG and 54–59.4 Gy for ependymoma patients. Patients who received craniospinal RT were not included. The eligible analysis cohort did not include patients with primary, subclinical, or underdetermined forms of hypothyroidism. Only patients with serial FT4 measurements after initiation of RT were eligible for analysis. The study was approved by the institutional review board.

Data collection

Sociodemographic and treatment data were retrospectively abstracted from medical and RT records. The earliest patients were treated on prospective therapeutic protocols that included evaluating pituitary–thyroid function by FT4 and TSH measurements. These assessments were standard in more recent patients, including those not enrolled in a prospective protocol. Patients received ongoing follow-up in the Radiation Oncology Clinic, followed by enrollment in a survivorship study for long-term monitoring and periodic follow-up appointments.[14] Neurocognitive testing was performed before RT treatment (baseline), at 6 months, and then yearly after RT for a total of 5 years and on indication by clinical referral.

Assays

From 1996 to 2018, reference ranges for FT4 and TSH concentrations changed thrice. Reference ranges for FT4 changed from 0.71–1.85 ng/dL (i.e., 9.1–23.8 pmol/L) to 0.8–2.0 ng/dL (i.e., 10.3–25.7 pmol/L) and then to 1.00–2.10 ng/dL (i.e., 12.9–27.0 pmol/L) from July 2005 onward. Corresponding upper limits of TSH concentrations were 5.0, 4.7 and 4.0 mIU/L, respectively, during these time periods. For longitudinal analysis, FT4 concentrations during these time periods were normalized to values between 1.0 and 2.10 ng/dL by using a location-scale model.[15] FT4 concentrations were measured by electro-chemiluminescent immunoassays, although different methods were used that required adjustments in reference ranges (before 2005, Ortho Clinical Diagnostics, Vitros; after 2005, Diagnostic Products Corporation, Immulite 2000). From 2005, the methodology for chemiluminescent immunoassay changed and did not require adjustment in reference ranges.

Diagnostic criteria for endocrine disorders

Diagnosis of central hypothyroidism was based on FT4 concentrations below the reference range and low or normal TSH concentrations. In a subset of patients, LT4 was started based on either clinical symptoms presumed to be caused by central hypothyroidism, and/or a blunted nocturnal

TSH surge, and/or an abnormal result after TRH testing.[16] The FT4 concentrations were within the reference range before start of LT4 in these patients, and they were therefore classified as having received "empirical LT4."

Diagnosis of primary hypothyroidism was based on elevated plasma TSH concentrations in combination with FT4 concentrations below the reference range. Subclinical hypothyroidism was defined by FT4 concentrations within the reference range in combination with elevated TSH concentrations.

Growth hormone deficiency (GHD) was defined as a GH peak response below 10 ng/mL after provocative testing in children up to the age of 16 years before January 2012 and below 5 ng/mL thereafter due to changes in the assay used. For children attaining their final height, a peak GH response below 3 ng/mL was considered abnormal.

Physical health outcomes

Definitions for height, weight, high fat mass, glucose disorder, and dyslipidemia are listed in Supplemental Table 1. A total of 6426 height z-scores (median 24 per patient, range 2–72) and 6428 weight z-scores (median 24 per patient, range 2–72) were included for longitudinal analysis.

Neurocognitive outcomes

Intellectual ability was estimated by using age-appropriate Wechsler scales. Due to high collinearity between Estimated Intellectual Quotient scores and Full Scale Intellectual Quotient scores, both scores were included to determine intelligence scores during follow-up.[17] Attention was assessed by the Conners' Continuous Performance Test; the omission score was used as a measure of sustained attention. Memory was assessed by total learning score from the age-appropriate version of the California Verbal Learning Test. Psychosocial functioning was assessed by parent-reported responses on the Child Behavior Checklist or Behavior Assessment System for Children, and internalizing index was used for analysis. All measures provide age-corrected scores based on large, representative standardization samples with well-established reliability and validity with respect to assessed cognitive abilities. Longitudinal neurocognitive measurements could be performed for 174 eligible patients (median 8 per patient, range 2–18).

Statistical analyses

A linear mixed-effects model with random intercept was fitted to examine longitudinal trends of FT4 since RT and to investigate the effects of demographic and treatment variables on these trends. All FT4 concentrations and longitudinal measurements of height, weight, and neurocognitive functioning up to the start of LT4, in case of diagnosed central hypothyroidism or empirical LT4, or tumor relapse if applicable and whichever occurred first, were included in the longitudinal analysis. The best-fitting model according to the Bayesian information criterion and

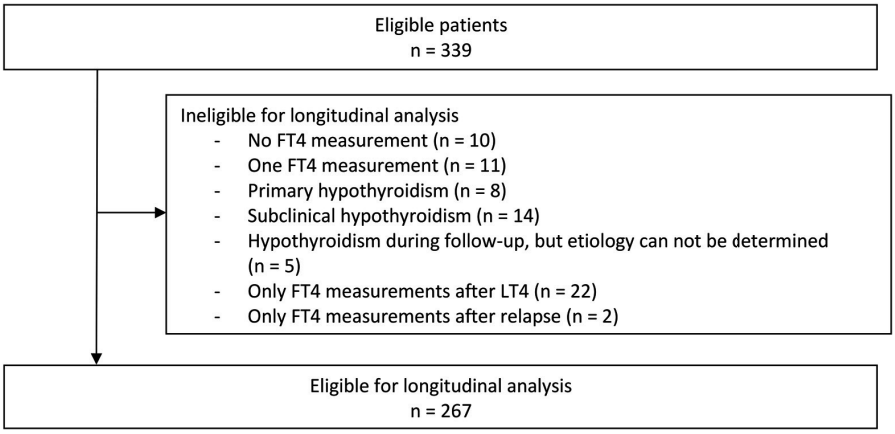
the most clinically meaningful multivariable model with demographic and treatment variables was constructed for risk factor analysis. For associations between FT4 concentrations and physical and neurocognitive outcomes, a two-stage mixed-effects model was used.[18] For these models, all longitudinal measurements of height, weight, and neurocognitive outcomes were included, whereas the last-available measurements were used to define high fat mass, glucose disorder, and dyslipidemia as dichotomized outcomes.

Results

Study population

Of 339 selected patients, 267 (78.8%) met the inclusion criteria for longitudinal analysis (Figure 1). Patients eligible for longitudinal analysis were more likely to be survivors of ependymoma, alive at last follow-up, less likely to have experienced relapse, and they received a higher initial dose of RT (Supplemental Table 2) than those not eligible for longitudinal analysis. Table 1 summarizes demographic and treatment characteristics for eligible patients. Median age at start of RT was 6.0 years (range 0.9–22.9) and median follow-up after RT exposure was 10.5 years (range 0.3–19.6).

Figure 1. Flow diagram of study cohort



Abbreviations: FT4; free thyroxine; LT4, thyroxine replacement therapy

Table 1. Demographic and treatment characteristics of patients

	Patients, n=267	
Variable	No.	%
Gender		
Male	133	49.8
Female	134	50.2
Race		
White	207	77.5
Black	40	15.0
Other	20	7.5
Current status		
No evidence of disease	106	39.7
Stable disease	98	36.7
Progression of disease	12	4.5
Deceased	51	19.1
Age at cancer diagnosis (years)	Median	Range
	4.53	0.20-22.76
Age at follow-up (years)	Median	Range
	17.76	2.84-40.47
Follow-up duration from RT (years)	Median	Range
	10.48	0.29-19.59
Primary tumor diagnosis		
Ependymoma	158	59.2
Low-grade glioma	109	40.8
Primary tumor location		
Suprasellar/supratentorial	102	38.2
Infratentorial	165	61.8
Hypothalamic-pituitary involvement		
Yes	72	27.0
No	195	73.0
Neurofibromatosis		
Yes	14	5.2
No	253	94.8
Hydrocephalus with or without shunt before RT		
Yes	146	54.7
No	121	45.3
Surgery before RT		
Yes	214	80.1

Table 1. Continued

	Patients, n=267	
Variable	No.	%
No	53	19.9
Chemotherapy before RT		
Yes	79	29.6
No	188	70.4
Alkylating agent before RT		
Yes	41	15.4
No	226	84.6
Age at start RT (years)	Median	Range
	5.97	0.89-22.93
Primary RT dose (Gy)	Median	Range
	59.40	50.4-59.4
Relapse after RT		
Yes	80	30.0
No	187	70.0

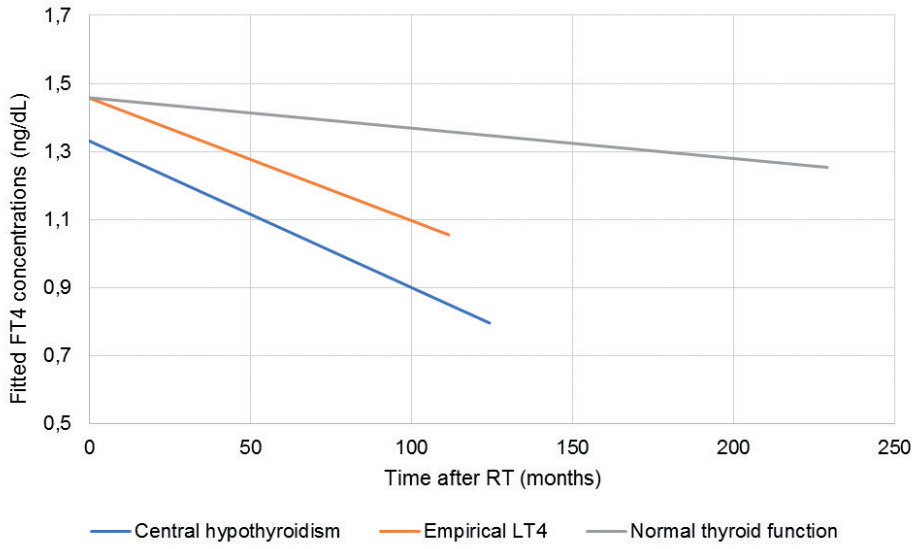
Abbreviations: Gy, gray; RT, radiation therapy

Longitudinal trends in FT4 concentrations by endocrine deficiencies

A total of 3197 FT4 measurements (median 11 per patient, range 2–32) were included in the longitudinal analysis. Of the 267 patients, 26 (9.7%) had central hypothyroidism, 32 (12.0%) received empirical LT4, and 209 (78.3%) had normal thyroid function during follow up. The longitudinal trend of FT4 modeled with time as the only variable revealed that FT4 concentrations significantly declined over time after start of RT (slope –0.00097 ng/dL per month; $P < 0.001$). Patients with central hypothyroidism had significantly lower baseline FT4 concentrations than did patients receiving empirical LT4 (P=0.012) and patients with normal thyroid function (P=0.001, Figure 2). Rates of FT4 decline were significantly higher in patients with central hypothyroidism (slope –0.00431 ng/dL per month) and those receiving empirical LT4 (slope –0.00360 ng/dL per month) than in patients with normal thyroid function (slope –0.00089 ng/dL per month; P<0.001 for slopes of central hypothyroidism and empirical LT4 groups compared with the group with normal thyroid function). Rates of FT4 decline were similar in patients with central hypothyroidism and those receiving empirical LT4 (P=0.449). Of 26 patients diagnosed with central hypothyroidism, 22 (84.6%) had central hypothyroidism at last follow-up whereas 4 (15.4%) had normal thyroid function without requiring LT4. Of 32 patients who received empirical LT4, 17 (53.1%) were euthyroid at last follow-up without requiring LT4. Of the remaining 15 (46.8%) patients, 2 still had empirical LT4 and in 13 the diagnosis of empirical LT4 was revised to central hypothyroidism (n=10) or primary hypothyroidism (n=3). Patients with GHD (n=102, 38.2%) had

higher baseline FT4 concentrations (P=0.034) and a significantly greater FT4 decline (P<0.001) than patients without GHD.

Figure 2. FT4 concentrations over time after start of irradiation in patients with central hypothyroidism, receiving empirical thyroxine treatment (LT4) and having normal thyroid function



Abbreviations: FT4; free thyroxine; RT, radiation therapy

Longitudinal trends in FT4 concentrations by demographic and treatment variables

Longitudinal trends in FT4 were modeled by univariable analysis for each of the following clinical variables: gender, race, HP tumor involvement, age at RT, alkylating agents before RT, hydrocephalus with or without shunt before RT, or age at last follow-up. Rates of FT4 decline were significantly higher in females than males (P<0.001), white race than black race (P=0.006), and patients with hydrocephalus than those without hydrocephalus (P=0.027). In addition, younger age of patients at RT (P<0.001) and follow-up (P<0.001) was associated with a higher rate of FT4 decline than older age of patients at RT and follow-up. At RT initiation, older patients and patients with HP tumor involvement had significantly lower baseline FT4 concentrations (both P<0.001) than did younger patients and those without HP tumor involvement. The best-fitting and most clinically meaningful multivariable model demonstrated significantly greater rates of FT4 decline in females than in males (P<0.001) and for younger age of patients than older age of patients at RT (P<0.001; Table 2). In multivariable analyses, patients with HP tumor involvement had a lower baseline of FT4 concentrations than did patients without HP tumor involvement (P=0.021). Older age of patients at RT was associated with lower baseline FT4 concentrations than was younger age of patients (P<0.001) when other included variables were fixed in the model.

Table 2. Multivariable linear mixed-effects modeling for demographic and treatment variables as predictors of baseline FT4 concentrations and FT4 decline

		Baseline			Rate of change		
Predictor	**Subgroup**	**Estimate**	**SE**	***P***	**Estimate**	**SE**	***P***
Gender	Male vs. female	-0.02334	0.0221	0.292	0.0009308	0.0001595	<0.001
HP tumor involvement	Yes vs. no	-0.06022	0.0259	0.021	-0.0001403	0.0002061	0.496
Age at start RT		-0.01558	0.002325	<0.001	0.0001637	0.0000184	<0.001

Abbreviations: Abbreviations: HP, hypothalamic-pituitary; RT, radiation therapy; SE, standard error

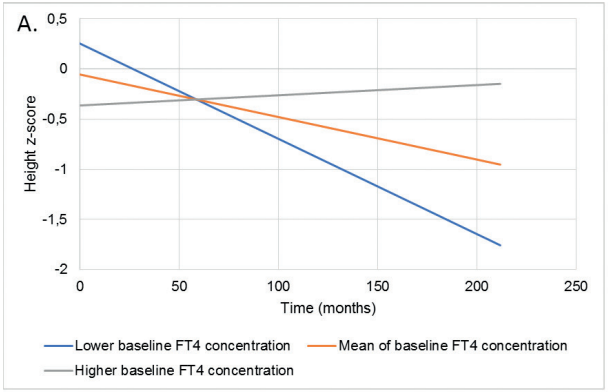
Longitudinal trends of FT4 concentrations by physical and neurocognitive outcomes

Overall, there was a significant decline in the rate of height z-score with FT4 decline ($P<0.001$). There was a significantly greater decline in the rate of height z-scores in patients with lower baseline FT4 concentrations ($P<0.001$, Figure 3A). Patients with smaller rates of decline in FT4 had higher rates of height z-scores ($P<0.001$, Figure 3B). Overall, rates of weight z-score increased significantly with FT4 decline ($P<0.001$), and lower baseline FT4 concentrations were associated with a higher increase in rates of weight z-scores at follow up ($P<0.001$, Figure 4A). The rate of weight gain increased with a greater rate of FT4 decline ($P<0.001$, Figure 4B). Patients with lower baseline FT4 concentrations had a significantly higher risk of glucose disorders (odds ratio[OR]=19.73, $P=0.002$) and dyslipidemia (OR=19.40, $P=0.003$) but not of high fat mass ($P=0.177$) than patients with higher FT4 concentrations. Decline in FT4 concentrations did not contribute to the occurrence of these 3 outcomes. Longitudinal patterns of neurocognitive functioning scores for intelligence, attention, and memory were not associated with baseline FT4 concentrations. Intelligence scores improved over time, although the rate of improvement was lower in patients with higher rates of FT4 decline ($P=0.014$). Patients with higher FT4 concentrations at baseline showed less improvement in parent-reported internalizing problems over time ($P=0.003$), but the rate of FT4 decline did not affect this outcome.

Discussion

This is the first study to longitudinally examine FT4 concentrations and its associations with clinical outcomes in a large and systematically assessed cohort of children and adolescents exposed to high-dose RT. FT4 concentrations declined significantly after start of RT and were independently associated with several patient- and tumor-related factors. This study is unique because phenotypic consequences of variation and trends in FT4 concentrations have not yet been longitudinally studied. We found that both lower baseline and declining FT4 concentrations were associated with adverse physical outcomes. Furthermore, changes in FT4 concentrations

Figure 3. Trends in height z-scores over time according to FT4 concentrations at baseline (A) and FT4 decline rates (B)



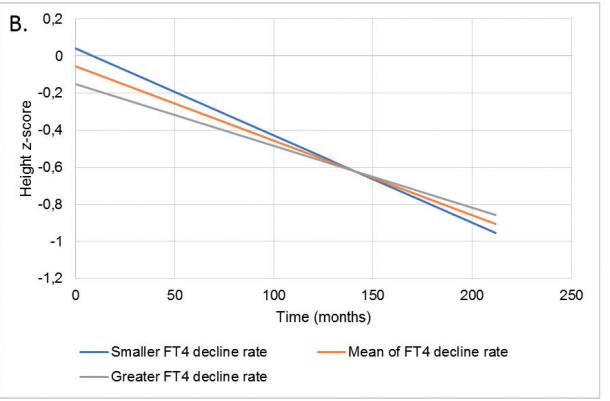
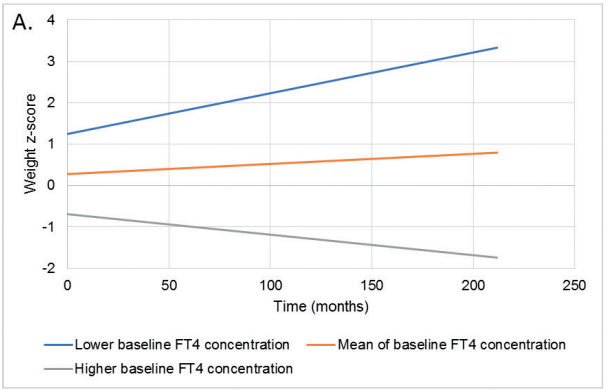
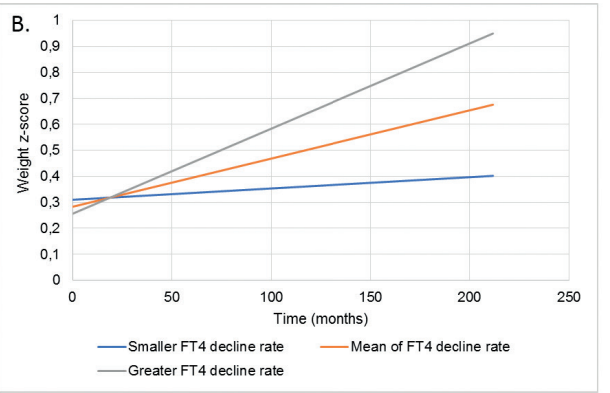


Figure 4. Trends in weight z-scores over time according to FT4 concentrations at baseline (A) and FT4 decline rates (B)





Abbreviations: FT4; free thyroxine

within the reference range did not have a major negative impact on neurocognitive functioning in our patients.

Few studies have reported thyroid hormone concentrations (free or total T4) over time in children exposed to RT. In a cross-sectional study, Lando et al. reported a significant total T4 decline of 1.5% per year after prophylactic cranial RT (15–24 Gy) in patients with acute lymphoblastic leukemia.[19] Another similar cross-sectional study reported a negative association between FT4 concentrations and follow-up time in patients with brain tumors exposed to high-dose RT.[20] However, the limitation of these cross-sectional approaches is that laboratory measurements and outcomes were simultaneously assessed and intra-individual changes remain unclear. A third study analyzing retrospective data on FT4 concentrations demonstrated significant FT4 decline (>25%) over time after RT, especially in patients with central hypothyroidism (>40%) during follow-up.[12] This study was limited by non-systematic assessments of FT4 concentrations and inclusion of patients with medulloblastoma, in whom thyroid function may also be affected by direct thyroid damage after craniospinal RT. Our longitudinal study that systematically assessed parameters of thyroid function supports with a higher degree of certainty that significant FT4 decline may occur after RT exposure in a large, homogeneous cohort. FT4 decline was more pronounced in patients who developed central hypothyroidism during follow up, but also occurred in patients in whom thyroid function remained within the reference range over time.

Cohort studies on the general pediatric population also show a significant decline in FT4 concentrations over time, although the rate of decline was lower (0.04 pmol/L in 2 years) than that in our study.[21] Rates of decline in the general pediatric population depended on baseline FT4 concentrations: those with higher FT4 concentrations at age 7 years were more likely to have substantial rates of decline over time at age 15 years than did children with lower FT4 concentrations at baseline. Our study found similar trends: patients who were older at start of RT had lower baseline FT4 concentrations and rates of FT4 decline than did younger patients. Higher rates of decline in younger patients in our cohort may also reflect higher susceptibility to RT damage in younger than older children.[22] Our study revealed no gender-specific differences in FT4 concentration at baseline, but the rate of FT4 decline for females was higher than for males. This result is unexpected, as no substantial gender-specific differences in FT4 concentrations have been reported in the general population and the prevalence of central hypothyroidism after RT exposure seems even higher in males than females.[23] Lower FT4 values at baseline for patients with HP involvement is not surprising, as it includes a high proportion of patients with LGG in the HP region. The HP region may have already been directly damaged before starting RT, leading to lower FT4 concentrations at baseline.[24]

Although interactions between different pituitary axes are beyond the scope of our analysis, higher FT4 values at baseline and steeper decline in FT4 concentrations with follow up in individuals with GHD are reported. Data on baseline FT4 concentrations in individuals with GHD are conflicting.[25] Although growth hormone (GH) can potentially suppress the TSH–T4 axis, the result of higher FT4 values at baseline should be validated in other cohorts. The more rapid decline in GH-deficient individuals with follow up may be due to GH replacement in a subset of patients. Decline in FT4 concentrations and unmasking of central hypothyroidism after initiating GH replacement therapy has been consistently reported.[26] Whether GH replacement, which is associated with more rapid FT4 decline, could also explain the slower rate of height loss paradoxically observed in individuals with a steeper FT4 decline requires additional investigation. Interactions between GH and the thyroid axis should ideally be investigated by a dedicated analysis incorporating data on FT4 deiodination and include timing of GHD onset and of GH replacement therapy.

A major strength of our study was the longitudinal examination of associations between FT4 concentrations and adverse health outcomes, which were previously lacking. Associations between impaired physical health and thyroid function have been reported in cross-sectional studies on the adult general population.[27,28] but not in children exposed to RT. We show that trends in FT4 concentrations in children exposed to RT are associated with changes in height and weight and also affect metabolic health with respect to glucose and lipid metabolism. The rate of FT4 decline was not associated with parameters of the metabolic syndrome. Note that outcomes of glucose disorder, dyslipidemia, and high fat mass were only defined at last follow up. Patients with highest rates of decline (i.e., those with central hypothyroidism) may have received LT4 during follow up, which could reverse any effects of trends in thyroid function on metabolic outcomes at last follow up. Future studies need to analyze whether continuous FT4 concentrations and FT4 trends, rather than strict population-based cut-off values, can better distinguish between euthyroid and hypothyroid states in individuals.

In our study, a subset of patients was empirically treated with LT4. Approximately 50% of these patients did not require LT4 during follow up to maintain normal FT4 concentrations, and it is unclear whether short-term LT4 in these patients resulted in improved physical outcomes. Whether survivors of childhood brain tumors, who are already at risk of the metabolic syndrome, would benefit from LT4 initiation at low to normal FT4 concentrations within the reference range should be studied further.

Associations between impaired neurocognitive health and thyroid function have been mainly reported in children with congenital forms of hypothyroidism.[29] Studies are lacking on neurocognitive development in children with acquired hypothyroidism. In our study, baseline FT4 concentrations were not associated with impaired neurocognitive outcomes. However, declining

FT4 concentrations were associated with worse intellectual performance over time while lower baseline FT4 concentrations were associated with improved psychosocial functioning. These observational data do not prove a causal association between FT4 concentrations and neurocognitive function. Our data suggest that changes of FT4 concentrations within the reference range do not have a major negative impact on neurocognitive functioning in this population.

Children and young adolescents exposed to RT are already at increased risk for adverse health outcomes.[30] Understanding the clinical significance of variation and trends in FT4 concentrations in this population will help formulate surveillance and treatment recommendations to initiate thyroid hormone replacement therapy. Current guidelines recommend yearly screening for central hypothyroidism in childhood cancer survivors, or more frequently during rapid growth, although high-quality evidence supporting this recommendation is lacking.[5,31] Our study suggests that low baseline or declining FT4 concentrations are associated with adverse physical outcomes. Close monitoring of thyroid function, especially in individuals with low or declining FT4 concentrations, is important for diagnosis and timely treatment of central hypothyroidism and might improve health outcomes in children exposed to RT.

Other strengths of our study include the large number of patients systematically and clinically followed for more than 10 years, high number of measurements that allowed robust longitudinal analysis of FT4 concentrations and trends, and assessment of unique associations between physical and neurocognitive health outcomes. Limitations of our study include the observational design that did not allow us to infer causality. In addition, clinical outcomes were not adjusted for other confounding factors associated with physical and neurocognitive outcomes, such as several cancer treatment modalities, GHD, and obesity. Furthermore, height and weight measurements were only available from January 2001 onward. Finally, associations between adverse cardiovascular outcomes (e.g., hypertension, heart failure and stroke) and higher FT4 concentrations could not be assessed due to the small number of events in a relatively young cohort.

In conclusion, our study demonstrates that FT4 concentration declines over time after high-dose RT exposure in children treated for a brain tumor and this decline seems to be associated with adverse physical health outcomes. Whether the diagnosis of central hypothyroidism and decision of initiating thyroid replacement therapy can be made by individual FT4 trends and rates of decline rather than by a FT4 concentration below the normal range needs to be examined in future studies.

References

1. Sklar CA, Constine LS. Chronic neuroendocrinological sequelae of radiation therapy. *Int J Radiat Oncol Biol Phys.* 1995;31(5):1113-1121.
2. Laughton SJ, Merchant TE, Sklar CA, et al. Endocrine outcomes for children with embryonal brain tumors after risk-adapted craniospinal and conformal primary-site irradiation and high-dose chemotherapy with stem-cell rescue on the SJMB-96 trial. *J Clin Oncol.* 2008;26(7):1112-1118.
3. Schmiegelow M, Feldt-Rasmussen U, Rasmussen AK, Poulsen HS, Muller J. A population-based study of thyroid function after radiotherapy and chemotherapy for a childhood brain tumor. *J Clin Endocrinol Metab.* 2003;88(1):136-140.
4. Brabant G, Toogood AA, Shalet SM, et al. Hypothyroidism following childhood cancer therapy-an under diagnosed complication. *Int J Cancer.* 2012;130(5):1145-1150.
5. Sklar CA, Antal Z, Chemaitilly W, et al. Hypothalamic-Pituitary and Growth Disorders in Survivors of Childhood Cancer: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2018;103(8):2761-2784.
6. Doin FC, Rosa-Borges M, Martins MR, Moises VA, Abucham J. Diagnosis of subclinical central hypothyroidism in patients with hypothalamic-pituitary disease by Doppler echocardiography. *Eur J Endocrinol.* 2012;166(4):631-640.
7. Klose M, Marina D, Hartoft-Nielsen ML, et al. Central hypothyroidism and its replacement have a significant influence on cardiovascular risk factors in adult hypopituitary patients. *J Clin Endocrinol Metab.* 2013;98(9):3802-3810.
8. Rose SR. Isolated central hypothyroidism in short stature. *Pediatr Res.* 1995;38(6):967-973.
9. Gruters A, Krude H. Detection and treatment of congenital hypothyroidism. *Nat Rev Endocrinol.* 2011;8(2):104-113.
10. Fleseriu M, Hashim IA, Karavitaki N, et al. Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2016;101(11):3888-3921.
11. Persani L, Brabant G, Dattani M, et al. 2018 European Thyroid Association (ETA) Guidelines on the Diagnosis and Management of Central Hypothyroidism. *Eur Thyroid J.* 2018;7(5):225-237.
12. van Iersel L, Clement SC, Schouten-van Meeteren AYN, et al. Declining free thyroxine levels over time in irradiated childhood brain tumor survivors. *Endocr Connect.* 2018.
13. Taylor PN, Razvi S, Pearce SH, Dayan CM. Clinical review: A review of the clinical consequences of variation in thyroid function within the reference range. *J Clin Endocrinol Metab.* 2013;98(9):3562-3571.
14. Hudson MM, Ness KK, Nolan VG, et al. Prospective medical assessment of adults surviving childhood cancer: study design, cohort characteristics, and feasibility of the St. Jude Lifetime Cohort study. *Pediatr Blood Cancer.* 2011;56(5):825-836.
15. Karvanen, J. (2003). The Statistical Basis of Laboratory Data Normalization. Drug Information Journal,37(1), 101-107. doi:10.1177/009286150303700112
16. Rose SR, Lustig RH, Pitukcheewanont P, et al. Diagnosis of hidden central hypothyroidism in survivors of childhood cancer. *J Clin Endocrinol Metab.* 1999;84(12):4472-4479.
17. Armstrong GT, Conklin HM, Huang S, et al. Survival and long-term health and cognitive outcomes after low-grade glioma. *Neuro Oncol.* 2011;13(2):223-234.
18. Chen YH, Ferguson KK, Meeker JD, McElrath TF, Mukherjee B. Statistical methods for modeling repeated measures of maternal environmental exposure biomarkers during pregnancy in association with preterm birth. *Environ Health.* 2015;14:9.
19. Lando A, Holm K, Nysom K, et al. Thyroid function in survivors of childhood acute lymphoblastic leukaemia: the significance of prophylactic cranial irradiation. *Clin Endocrinol (Oxf).* 2001;55(1):21-25.

20. Constine LS, Woolf PD, Cann D, et al. Hypothalamic-pituitary dysfunction after radiation for brain tumors. *N Engl J Med.* 1993;328(2):87-94.

21. Taylor PN, Sayers A, Okosieme O, et al. Maturation in Serum Thyroid Function Parameters Over Childhood and Puberty: Results of a Longitudinal Study. *J Clin Endocrinol Metab.* 2017;102(7):2508-2515.

22. Vatner RE, Niemierko A, Misra M, et al. Endocrine Deficiency As a Function of Radiation Dose to the Hypothalamus and Pituitary in Pediatric and Young Adult Patients With Brain Tumors. *J Clin Oncol.* 2018;36(28):2854-2862.

23. Clement SC, Schouten-van Meeteren AY, Boot AM, et al. Prevalence and Risk Factors of Early Endocrine Disorders in Childhood Brain Tumor Survivors: A Nationwide, Multicenter Study. *J Clin Oncol.* 2016;34(36):4362-4370.

24. Merchant TE, Williams T, Smith JM, et al. Preirradiation endocrinopathies in pediatric brain tumor patients determined by dynamic tests of endocrine function. *Int J Radiat Oncol Biol Phys*. 2002;54(1):45-50.

25. Agha A, Walker D, Perry L, et al. Unmasking of central hypothyroidism following growth hormone replacement in adult hypopituitary patients. *Clin Endocrinol (Oxf).* 2007;66(1):72-77.

26. Giavoli C, Profka E, Rodari G, Lania A, Beck-Peccoz P. Focus on GH deficiency and thyroid function. *Best Pract Res Clin Endocrinol Metab.* 2017;31(1):71-78.

27. Knudsen N, Laurberg P, Rasmussen LB, et al. Small differences in thyroid function may be important for body mass index and the occurrence of obesity in the population. *J Clin Endocrinol Metab.* 2005;90(7):4019-4024.

28. Garduno-Garcia Jde J, Alvirde-Garcia U, Lopez-Carrasco G, et al. TSH and free thyroxine concentrations are associated with differing metabolic markers in euthyroid subjects. *Eur J Endocrinol.* 2010;163(2):273-278.

29. Leger J, Olivieri A, Donaldson M, et al. European Society for Paediatric Endocrinology consensus guidelines on screening, diagnosis, and management of congenital hypothyroidism. *J Clin Endocrinol Metab.* 2014;99(2):363-384.

30. Bhakta N, Liu Q, Ness KK, et al. The cumulative burden of surviving childhood cancer: an initial report from the St Jude Lifetime Cohort Study (SJLIFE). *Lancet.* 2017;390(10112):2569-2582.

31. Children's Oncology Group. Long-term follow-up guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancer. Version 5.0, 2018. Available from http://www.survivorshipguidelines.org/pdf/2018/COG_LTFU_Guidelines_v5.pdf (accessed February 4, 2019).

Supplementary material

Supplemental Table 1. Definitions of physical outcomes

Physical outcome	Definition
Height	Age and gender adjusted z-score for patients aged <20 years
Weight	Age and gender adjusted z-score for patients aged <20 years
High fat mass	Total fat grams divided by total mass grams as measured by whole body dual-energy x-ray absorptiometry scans with a QDR 4500 fan-array scanner (Hologic, Inc, Bedford, Mass), and expressed as percentage. High fat mass was defined as a body fat percentage ≥ 25% in males, and ≥ 30% in females.
Glucose disorder	Glucose disorder was defined as either an elevated fasting insulin level (i.e. insulin ≥118 pmol/L or ≥17 mIU/L), impaired glucose tolerance (i.e. glucose ≥7.8 mmol/L or 140 mg/dL), overt diabetes mellitus type 2 and/or treatment with glucose-lowering medications. Patients with a morning glucose ≥5.6 mmol/L (or 100 mg/dL), but <7.8 mmol/L were excluded, as the fasting state during blood withdrawal could not be determined for all patients.
Dyslipidemia	Fasting cholesterol, triglycerides, and high- or low-density lipoproteins were measured using an enzymatic spectrophotometric assay (Roche Modular P Chemistry Analyzer; Roche Diagnostics). Dyslipidemia was defined as either a total cholesterol ≥5.2 mmol/L (or ≥200 mg/dL), low-density lipoprotein ≥3.4 mmol/L (or ≥130 mg/dL), high-density lipoprotein <1.0 mmol/L (or <40 mg/dL), triglycerides ≥1.7 mmol/L (or ≥150 mg/dL) and/or use of lipid lowering medications. Patients on active therapy were excluded for this analysis, due to potential treatment-induced dyslipidemia.

Supplemental Table 2. Demographic and treatment characteristics of eligible and non-eligible patients

	Eligible patients, n=267		Non-eligible patients, n=72		p-value
Variable	No.	%	No.	%	
Gender					
Male	133	49.8	42	58.3	0.199
Female	134	50.2	30	41.7	
Race					
White	207	77.5	55	76.4	0.321
Black	40	15.0	8	11.1	
Other	20	7.5	9	12.5	
Current status					
No evidence of disease	106	39.7	21	29.2	0.025
Stable disease	98	36.7	28	38.9	
Progression of disease	12	4.5	0	0.0	
Deceased	51	19.1	23	31.9	
Age at cancer diagnosis (years)	Median	Range	Median	Range	
	4.53	0.20- 22.76	4.44	0.30-24.63	0.581
Age at follow-up (years)	Median	Range	Median	Range	
	17.76	2.84-40.47	17.75	2.02-36.91	0.462
Follow-up duration from RT (years)	Median	Range	Median	Range	
	10.48	0.29-19.59	9.78	0.12-18.97	0.416
Primary tumor diagnosis					
Ependymoma	158	59.2	32	44.4	0.025
Low-grade glioma	109	40.8	40	55.6	
Primary tumor location					
Suprasellar/supratentorial	102	38.2	29	40.3	0.748
Infratentorial	165	61.8	43	59.7	
Hypothalamic-pituitary involvement					
Yes	72	27.0	22	30.6	0.546
No	195	73.0	50	69.4	
Neurofibromatosis					
Yes	14	5.2	4	5.6	1.000
No	253	94.8	68	94.4	

Table 2. Continued

	Eligible patients, n=267		Non-eligible patients, n=72		p-value
Variable	No.	%	No.	%	
Hydrocephalus with or without shunt before RT					
Yes	146	54.7	42	58.3	0.580
No	121	45.3	30	41.7	
Surgery before RT					
Yes	214	80.1	53	73.6	0.229
No	53	19.9	19	26.4	
Chemotherapy before RT					
Yes	79	29.6	25	34.7	0.487
No	188	70.4	47	65.3	
Alkylating agent before RT					
Yes	41	15.4	11	15.3	0.987
No	226	84.6	61	84.7	
Age at start RT (years)	Median	Range	Median	Range	
	5.97	0.89-22.93	7.59	1.06-24.91	0.074
Primary RT dose (Gy)	Median	Range	Median	Range	
	59.4	50.4-59.4	54.0	50.4-59.4	0.008
Relapse after RT					
Yes	80	30.0	31	43.1	0.036
No	187	70.0	41	56.9	

Abbreviations: Gy, gray; RT, radiation therapy

9

Recommendations for surveillance of hypothalamic-pituitary dysfunction for childhood, adolescent and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group

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*Shared last authorship

In progress

Abstract

Introduction

Hypothalamic-pituitary (HP) dysfunction in childhood, adolescent and young adult (CAYA) cancer survivors can result from tumor or treatment perturbations that include cranial radiotherapy and surgery. Substantial differences among current surveillance recommendations may prevent appropriate and timely screening and referral of CAYA cancer survivors. The International Late Effects of Childhood Cancer Guideline Harmonization Group aims to develop recommendations for surveillance of HP dysfunction in CAYA cancer survivors.

Methods

Existing surveillance recommendations, in combination with evidence identified by a systematic MEDLINE search and expert opinion, were synthesized to formulate and harmonize recommendations by a guideline panel including 42 multidisciplinary international experts. Recommendations were graded according to the strength of underlying evidence and considerations of potential benefits and harms of early detection and appropriate management.

Results

The guideline panel reviewed the identified studies, developed evidence summaries, appraised the quality of the body of evidence and formulated recommendations covered by four topics: (1) Who needs surveillance?; (2) When should surveillance be initiated? At what frequency and for how long should surveillance be performed?; (3) What surveillance modality should be used?; and (4) What should be done when abnormalities are identified?

Conclusion

The harmonized surveillance recommendations for HP dysfunction are based on a transparent process and are intended to positively influence health outcomes and facilitate care for CAYA cancer survivors. Data informing this guideline underscore the paucity of high-quality evidence and need for further targeted research.

Introduction

Survival rates for childhood cancer have substantially improved during the past decades, with an estimated 5-year survival exceeding 80%.[1,2] The consequences of cancer survivorship include a lifelong increased risk for morbidity and mortality related to late effects of cancer and cancer treatment.[3] Endocrine disorders are among the most common late effects, and are reported in up to 40-50% of survivors of childhood, adolescent and young adult (CAYA) cancer during their lifetimes.[4] Hypothalamic-pituitary (HP) dysfunction may result from local tumor invasion or injury following radiation and/or surgery.[5,6] HP dysfunction may manifest as growth hormone deficiency (GHD), thyroid stimulating hormone deficiency (TSHD), luteinizing hormone/follicle-stimulating hormone deficiency (LH/FSHD), adrenocorticotropic hormone deficiency (ACTHD), and central precocious puberty (CPP), with potential negative effects on final height attainment, pubertal development, body composition, and general well-being. As such, HP injury is associated with substantial adverse physical and psychosocial consequences.[5,7]

CAYA cancer survivors, and their health-care providers may benefit from guidelines that facilitate identification of HP dysfunction, which allows timely treatment. Clinical practice guidelines have been developed by North American and European groups for long-term surveillance for HP dysfunction in CAYA cancer survivors.[8-11] Consensus across these guidelines is lacking for at-risk populations, including the risk associated with specific cranial RT doses, the timing of initiation and frequency of screening, and surveillance modalities. Because these inconsistencies may hinder the implementation of surveillance across international settings and provision of clinically effective care, the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) was developed to harmonize existing guidelines and establish global consensus. Herein, we summarize the evidence and recommendations for surveillance of HP dysfunction in CAYA cancer survivors.

Methods

Guideline development panel

For this guideline, a core group was assembled consisting of 42 representatives from the North American Children's Oncology Group (COG), Dutch Childhood Oncology Group (DCOG), Scottish Intercollegiate Guidelines Network (SIGN), United Kingdom Children's Cancer and Leukaemia Group (UKCCLG), and experts in the fields of pediatric oncology and hematology, endocrinology, radiation oncology, neurosurgery, survivorship care and epidemiology. Recommendations from the COG, DCOG, SIGN and UKCCLG guidelines were extracted and evaluated for concordances and discordances (Table 1).[8-11] Clinical questions for items that were discordant across guidelines were formulated and covered the following key issues: Who needs surveillance (working group (WG) 1)?; When should surveillance be initiated? At what frequency and for how long should

surveillance be performed (WG 2)?; What surveillance modality should be used (WG 3)?; and What should be done when abnormalities are identified (WG 4, Supplementary material)?

Scope

The scope of this guideline is to (1) define surveillance strategies for HP dysfunction in CAYA cancer survivors, diagnosed with cancer up to 25 years of age, at the end of cancer treatment or with stable residual disease and without pre-existing HP dysfunction (2) define surveillance strategies for HP dysfunction occurring as a late effect after treatment for childhood cancer and not acutely at cancer diagnosis or perioperatively; and (3) provide guidance to oncology or late effects clinic providers in regards to subsequent steps following a positive screen, including indications for specialized endocrine referrals, but excluding disease management. The scope of these recommendations does not include individuals with a history of craniopharyngioma or other pituitary tumors, and those with known, pre-existing HP dysfunction. These individuals should all be seen by an (pediatric) endocrinologist.

Systematic literature review and definitions

We did systematic searches of the medical literature for studies of CAYA cancer survivors. We searched MEDLINE (through PubMed) between January 1990 and November 8, 2018. Search terms included "childhood cancer", "radiotherapy", "chemotherapy", "neurosurgery", "hypopituitarism", "pituitary hormones", "growth hormone", thyroid stimulating hormone", "adrenocorticotropic hormone", "follicle stimulating hormone", "luteinizing hormone", and "precocious puberty" (detailed search strategy is provided in the Supplementary material). We also contacted experts from the panel to determine if any additional evidence was available. Only reports published in English were reviewed. The inclusion criteria were based on study population, outcomes and type of study (Supplementary material). Eligible study populations were CAYA cancer survivors, in which 75% or more had been diagnosed with cancer. Eligible outcomes included five types of HP dysfunction: GHD, TSHD, LH/FSHD, ACTHD and CPP. Studies reporting on hypopituitarism in general, were excluded. All study designs were eligible if the sample size included at least 20 patients and if the study included a multivariable analysis for WG1; if the sample size included at least 20 patients diagnosed with HP dysfunction and the study reported use of a screening protocol as indication for longitudinal follow-up for WG2; if the sample size included at least 20 patients who received hormonal treatment for WG4. For WG3, we did not apply restrictions on the sample size. When evidence was lacking for CAYA cancer survivors, we carefully extrapolated evidence from existing guidelines for diagnosis or treatment of HP dysfunction in the general population.

Table 1. Concordance and discordance among existing hypothalamic-pituitary dysfunction guidelines

	North American Children's Oncology Group	Dutch Childhood Oncology Group	UK Children's Cancer and Leukaemia Group	Scottish Intercollegiate Guidelines Network	Concordance and discordance
Who needs surveillance?					
Cranial RT	Yes	Yes	Yes	Yes	Concordant
TBI	Yes (GHD)	Yes (GHD)	Yes (not specified)	Yes (not specified)	Discordant
Higher RT dose	Yes GHD: TBI ≥10 Gy (single fraction), ≥ 12 Gy (fractionated), cranial RT ≥ 18 Gy TSHD: cranial RT ≥ 40 Gy LH/FSHD: cranial RT ≥ 30 Gy ACTHD: cranial RT ≥ 30 Gy CPP: cranial RT ≥ 18 Gy	Yes GHD: cranial RT and TBI TSHD: only specified for all forms of thyroid problems LH/FSHD: all survivors (gonadal axis) ACTHD: cranial RT ≥ 50 Gy or lower dose and failure of other types of HP dysfunction CPP: all survivors (gonadal axis)	Yes Cranial RT/TBI, not specified per HP axis	Yes Cranial RT for all HP-axes Effects on HP function after TBI	Discordant
Chemotherapy	Not stated	Not stated	Not stated	Not stated	Discordant
Surgery in the suprasellar region	Yes	Not stated	Not stated	Not stated	Discordant
Brain tumor	Yes, in hypothalamic or hypophyseal area	Yes, in hypothalamic or hypophyseal area	Yes, not specified	Yes, craniopharyngioma	Concordant
History of hydrocephalus	Not stated	Not stated	Not stated	Not stated	Discordant

Table 1. Continued

	North American Children's Oncology Group	Dutch Childhood Oncology Group	UK Children's Cancer and Leukaemia Group	Scottish Intercollegiate Guidelines Network	Concordance and discordance
When should surveillance be initiated? At what frequency and for how long should surveillance be performed?					
Initiation of surveillance	Not stated	Not stated	Not stated	After completion of treatment (thyroid function)	**Discordant**
Duration of surveillance	Not stated	Not stated	Not stated	CCS are likely to require lifetime surveillance (TSHD)	**Discordant**
Surveillance frequency	GHD: every six months until growth is completed or until sexually mature, then yearly TSHD: yearly, or more often if rapid growth LH/FSHD: yearly for Tanner staging, until sexually mature ACTHD: yearly CPP: yearly, until sexually mature	GHD: ≤18 years annually, >18 years once per 3 years TSHD: ≤18 years annually, >18 years once per 2-3 years LH/FSHD and CPP: every LATER outpatient visit ACTHD: if clinical suspicion or presence of other types of HP dysfunction, in any case once 5 years after diagnosis	Every six months until growth is completed (for height, weight, Tanner staging)	Regular until final height, close monitoring for clinical signs of CPP TSHD: regular thyroid function after completion of treatment	**Discordant**

Abbreviations: ACTHD, adrenocorticotropic hormone deficiency; CCS, childhood cancer survivors; CPP, central precocious puberty; FT4, free thyroxine; FSH, follicle stimulating hormone; GHD, growth hormone deficiency; Gy, gray; HP, hypothalamic-pituitary; IGF-1, insulin-like growth factor 1; LH, luteinizing hormone; LH/FSHD, luteinizing hormone/follicle-stimulating hormone deficiency; RT, radiation therapy; TBI, total body irradiation; TSH, thyroid stimulating hormone; TSHD, thyroid stimulating hormone deficiency

Table 1. Continued

	North American Children's Oncology Group	Dutch Childhood Oncology Group	UK Children's Cancer and Leukaemia Group	Scottish Intercollegiate Guidelines Network	Concordance and discordance
What surveillance modality should be used?					
History	Nutritional status, fatigue weight gain, cold intolerance, constipation, dry skin, brittle hair, depressed mood, pubertal onset and tempo, sexual function (♂ erections, nocturnal emissions, ♀ vaginal dryness), libido, menstrual/ pregnancy history, failure to thrive, anorexia, dehydration, hypoglycaemia, lethargy, unexplained hypotension, medication use	Not stated	Not stated	Not stated	Discordant
Physical examination	Height	Growth chart (≤ 18 years)	Height (and chart)	Height (plotted onto growth charts)	Concordant
Physical examination	Pubertal staging, testicular volume by Prader orchidometry in boys	Pubertal staging, including testicular volume in boys (before and during puberty)	Pubertal staging (orchidometer in boys)	Pubertal staging	Concordant
Physical examination	Weight, BMI, hair, skin, thyroid exam	Thyroid exam	Weight, sitting height, bone age (consider annually)	Sitting height and bone age. These should be plotted onto growth charts	Discordant
Laboratory measurements	TSH, FT4, FSH, LH, testosterone ♂ (ideally morning), estradiol ♀, semen analysis at request	IGF-1, TSH, FT4, plasma morning cortisol concentration, if clinically indicated: LH, FSH, estradiol, testosterone	Not stated	Thyroid function	Discordant
What should be done when abnormalities are identified?					
Counselling	Yes	Yes	Not stated	Not stated	Discordant
Refer to endocrinologist	Yes	Yes	Yes	Not stated	Discordant

Selection of studies was performed independently by two reviewers. Detailed information from each selected study was extracted and reported into single evidence tables. The evidence tables were used to generate summary of findings tables. Evidence was appraised using GRADE.[12] (Supplementary material).

From evidence to recommendations.
Recommendations were based on data presented in the evidence summaries, combined with other considerations including clinical judgment, costs, benefits versus harms of the surveillance intervention, and the need to maintain flexibility of application across different health-care systems. The strength of the recommendations was graded according to published evidence-based methods (Supplementary material).[13,14]

Results

In total, 15 studies reporting on risk factors were included for WG1, 17 reporting on latency times and risk over time for WG2, 7 reporting on the diagnostic value of surveillance tests for WG3, and 12 reporting on benefits and harms of treatment interventions for WG4 (Figures 1A-D). The conclusions and quality of evidence and recommendations are summarized in Tables 2 and 3.

Who needs surveillance for HP dysfunction?

Evidence for radiation therapy exposing the HP region
Included studies for WG1 were divided among CAYA cancer survivors with and without central nervous system (CNS) tumors. The latter category includes CAYA cancer survivors treated for non-CNS tumors of the head or neck, leukemia and/or individuals with a history of stem cell transplantation. Individuals surviving CNS tumors or non-CNS tumors of the head or neck are frequently exposed to RT doses above 36 Gy. CAYA cancer survivors with a history of leukemia or individuals who received stem cell transplantation, have been usually treated with RT doses less than 14 Gy in case of total body irradiation (TBI), or prophylactic cranial RT with doses ranging between 18 to 24 Gy.

In CAYA cancer survivors of CNS tumors, high (GHD[6,15-17]), moderate (ACTHD[6,16]), and low (TSHD[15], LH/FSHD[16], CPP[15]) quality evidence support that RT exposing the HP region is associated with an increased risk of HP dysfunction. In this population, increasing doses of RT were associated with increased risks for GHD[18-20] (high quality evidence) and ACTHD[21] (low quality evidence). We did not identify studies with our selection criteria that have assessed the risk of RT dose on the other types of HP dysfunction.

Figure 1A. Flow chart of selected studies for WG1

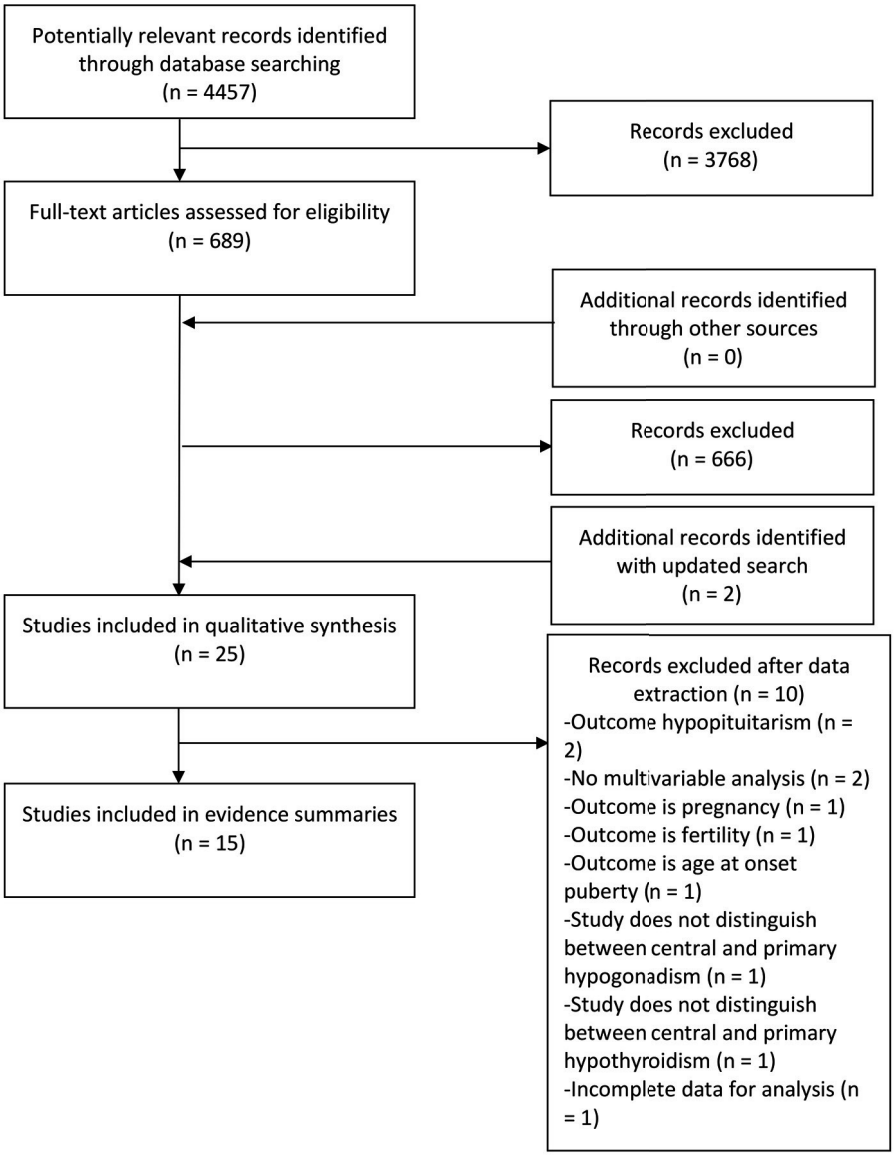


Figure 1B. Flow chart of selected studies for WG2

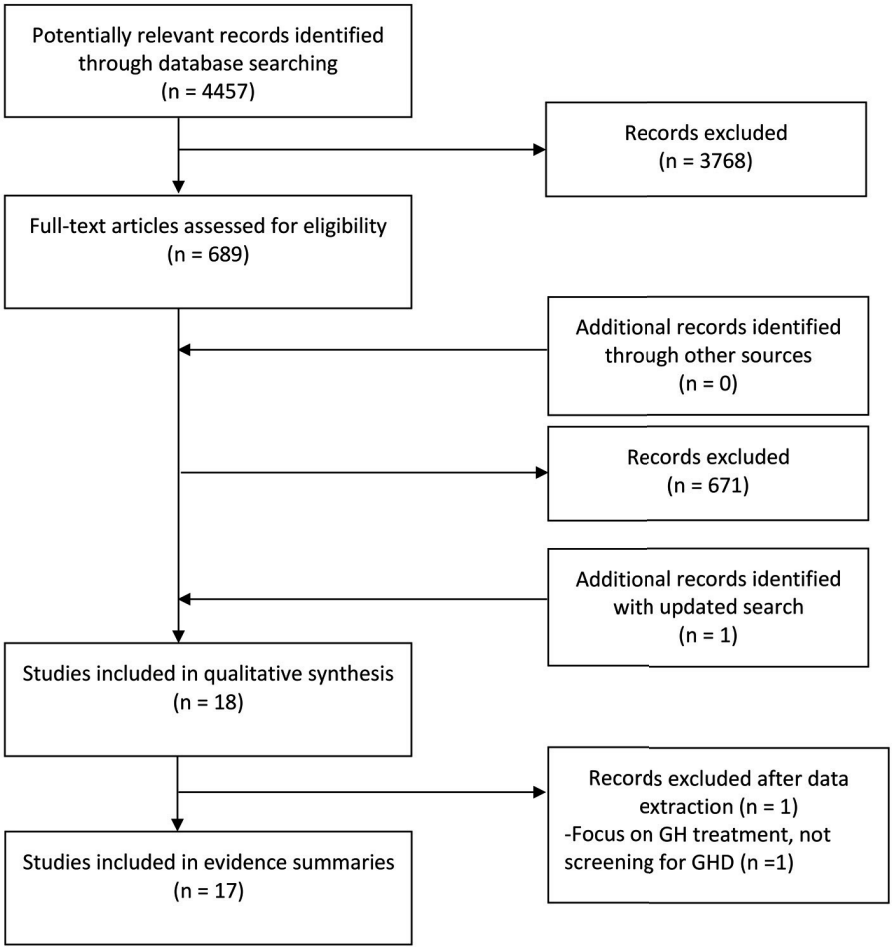


Figure 1C. Flow chart of selected studies for WG3

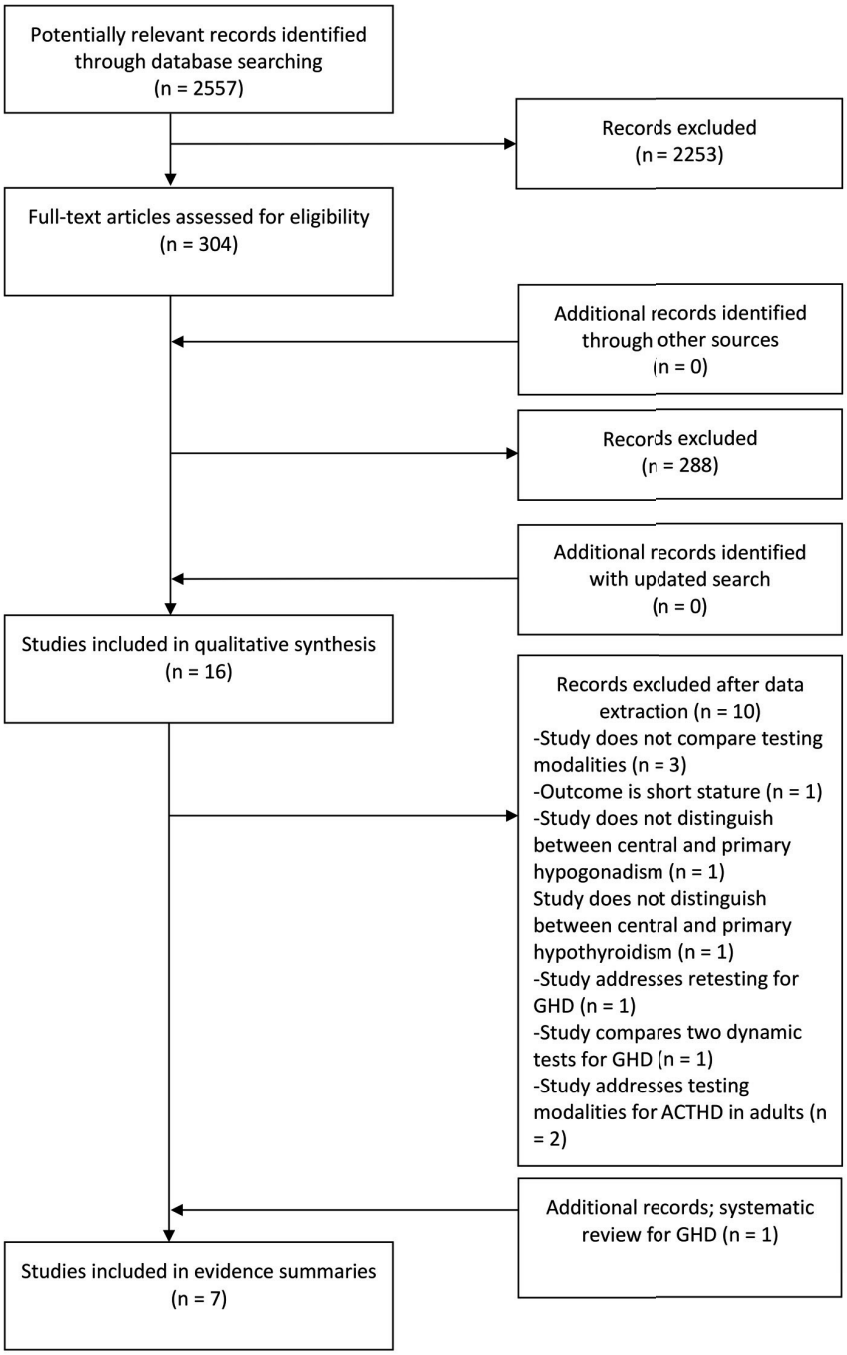
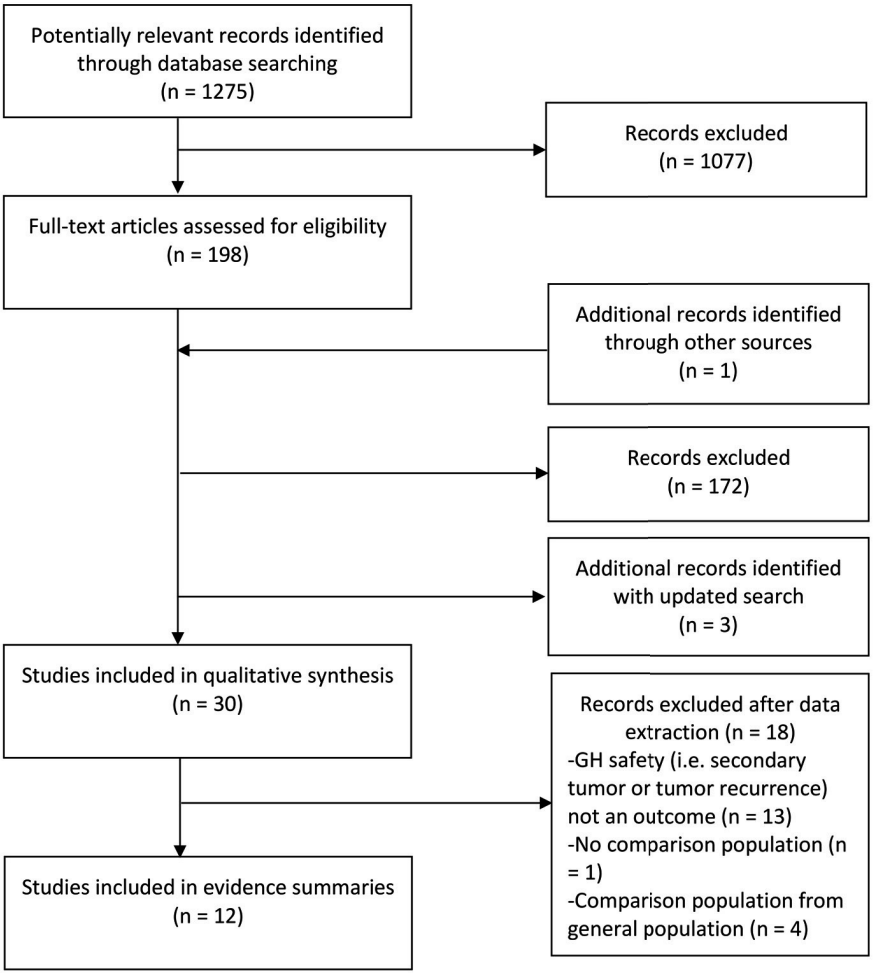


Figure 1D. Flow chart of selected studies for WG4



In CAYA cancer survivors without CNS tumors, there is high quality evidence that RT exposing the HP region, including TBI, is associated with an increased risk of GHD[22-24]. TBI was associated with an increased risk for GHD in two studies (very low quality evidence)[23,24], but no studies were identified for TBI as a risk exposure for TSHD, ACTHD, LH/FSHD, and CPP. Higher doses of RT exposing the HP region have been shown to expose CAYA cancer survivors to higher risks for GHD[5,25,26], TSHD[5], LH/FSHD[5] (moderate quality evidence) and ACTHD (low quality evidence)[5]. When assessing different modalities of RT, we did not find a different risk after proton RT compared to photon RT for GHD[27] (very low quality evidence). With our study selection criteria, we did not identify studies on the risk of HP dysfunction after different fractionation schedules.

Evidence for tumors near or within the HP region

The existing surveillance recommendations are concordant regarding the increased risk for HP dysfunction in CAYA cancer survivors with CNS tumors near or within the HP region.

Evidence for neurosurgery near or within the HP region

There is low quality evidence that neurosurgery in general is not associated with an increased risk for GHD[6,15], TSHD[15], ACTHD[6] or CPP[15] in cohorts including CAYA cancer survivors with and without CNS tumors near or within the HP region. There is low quality evidence that a higher number of neurosurgeries is associated with a higher risk of GHD[16], compared to lower number of neurosurgeries in a cohort of CAYA cancer survivors with CNS tumors near or within the HP region. No studies were identified that evaluated the risk of LH/FSHD after neurosurgery.

Evidence for chemotherapy

Studies showed that chemotherapy does not increase the risk for GHD[6,20] (high quality evidence), ACTHD[6,16,21] (moderate quality evidence) and CPP[16] (low quality evidence). We did not identify studies reporting on risk associations between chemotherapy and TSHD and LH/FSHD.

Evidence for hydrocephalus

There is low quality evidence that hydrocephalus or cerebrospinal fluid (CSF) shunting is associated with a higher risk for GHD[15,19] and CPP[15]. There is low quality evidence that hydrocephalus does not increase the risk of TSHD[15]. No studies were identified that evaluated the risk of ACTHD and LH/FSHD after hydrocephalus.

Evidence for brain injury

No studies were identified that evaluated the risk of HP dysfunction after brain injury in CAYA cancer survivors (defined as increased intracranial pressure, meningitis, cerebral thrombosis, cerebral haemorrhage, brain abscess, encephalopathy, cerebral inflammation or encephalitis).

Considerations of evidence that led to decision making regarding recommendations

Exposure of the HP region to RT increases the risk for HP dysfunction. However, with our study selection criteria, no evidence was found for a specific threshold RT dose. The guideline panel did not define a specific cut-off for surveillance of HP dysfunction to address discordances among the existing guidelines, but recognize based on clinical experience and evidence from historic studies that the doses of RT associated with GHD are lower than those associated with TSHD, LH/FSHD and ACTHD.[28] We identified no literature to support that neurosurgical procedures are associated with the occurrence of HP dysfunction as a late effect; data pertaining specifically to procedures involving the HP region were however limited. Nevertheless, the panel believes that CAYA cancer survivors with CNS tumors, or surgery near or within the HP region are prone for HP dysfunction and such individuals should receive surveillance. Although we identified only low quality evidence that hydrocephalus or CSF shunts are associated with a higher risk for GHD and CPP, this association is further supported by studies in non-cancer populations.[29]

Recommendations for high-risk groups of HP dysfunction

Surveillance for HP dysfunction is recommended for all CAYA cancer survivors treated with RT exposing the HP region (high quality evidence for GHD, strong recommendation; moderate quality evidence for ACTHD, strong recommendation; low quality evidence for TSHD, LH/FSHD and CPP, strong recommendations), CNS tumors near or within the HP region (high quality evidence and expert opinion, strong recommendation), and surgery near or within the HP region (expert opinion, strong recommendation). Surveillance for GHD is reasonable for CAYA cancer survivors treated with TBI (very low quality evidence, moderate recommendation). Surveillance for GHD is reasonable (low quality evidence and expert opinion, moderate recommendation), but is recommended for CPP (low quality evidence and expert opinion, strong recommendation) for CAYA cancer survivors with a history of hydrocephalus or CSF shunt.

Table 2. Conclusions of evidence from the systematic literature search for hypothalamic-pituitary dysfunction surveillance for childhood, adolescent and young adult (CAYA) cancer survivors (CNS tumor and non-CNS tumor)

1. Who needs surveillance?	
Risk GHD in CAYA cancer survivors (CNS tumor)	**Quality of evidence**
Increased risk after *cranial radiotherapy* vs. no cranial radiotherapy	⊕⊕⊕⊕ HIGH [6,15-17]
Increased risk after *higher doses of cranial radiotherapy* vs. lower doses	⊕⊕⊕⊕ HIGH [18-20]
Unknown risk after different *fractionation schedules*	No studies
No significant effect after different *types of radiotherapy (proton vs. photon)*	⊕⊖⊖⊖ VERY LOW [27]
No significant effect of *spinal radiotherapy* vs. no spinal radiotherapy	⊕⊖⊖⊖ VERY LOW [17]

No significant effect of *chemotherapy* vs. no chemotherapy in addition to cranial radiotherapy	⊕⊕⊕⊕ HIGH [6,20]
Unknown risk after *chemotherapy* vs. no chemotherapy, without exposure to radiotherapy	No studies
No increased risk after *neurosurgery* vs. *no neurosurgery*	⊕⊕⊖⊖ LOW [6 15]
Increased risk after higher number of neurosurgeries vs. lower number	⊕⊕⊖⊖ LOW [16]
Increased risk in *males* vs. females	⊕⊕⊖⊖ LOW [15,20,27]
No significant effect of *neurofibromatosis*	⊕⊕⊖⊖ LOW [6]
Increased risk after *hydrocephalus* or CSF shunt vs. no hydrocephalus or CSF shunt	⊕⊕⊖⊖ LOW [15,19]
Increased risk after *younger age at tumor diagnosis/treatment* vs. older age	⊕⊕⊖⊖ LOW [15,17,18,20,27]
Increased risk after *longer follow-up* vs. shorter follow-up	⊕⊕⊖⊖ LOW [15,18-20]
Increased risk in *later treatment era* vs. earlier treatment era	⊕⊕⊕⊖ MODERATE [16]
Unknown risk for different *ethnicities/races, different histologies/types, genetic profiles*, *age at follow-up*	No studies
Risk GHD in CAYA cancer survivors (non-CNS tumor)	**Quality of evidence**
Increased risk after *radiotherapy to the head and neck region* vs. no radiotherapy	⊕⊕⊕⊕ HIGH [22-24]
Increased risk after *higher doses of radiotherapy to the head and neck region* vs. lower doses	⊕⊕⊕⊖ MODERATE [5,25,26]
Increased risk after *total body irradiation* vs. no total body irradiation	⊕⊖⊖⊖ VERY LOW [23,24]
Unknown risk after different fractionation schedules, types of radiotherapy and spinal radiotherapy	No studies
Unknown risk after *chemotherapy* with or without exposure to radiotherapy	No studies
Unknown risk after *brain injury* vs. no brain injury	No studies
No significant effect of different *ethnicities/races*	⊕⊕⊖⊖ LOW [5]
Increased risk after *younger age at tumor diagnosis/treatment* vs. older age	⊕⊕⊖⊖ LOW [5,25,26]
Increased risk after *younger age at follow-up* vs. older age	⊕⊕⊖⊖ LOW [5,24]
Increased risk after *longer follow-up* vs. shorter follow-up	⊕⊖⊖⊖ VERY LOW [24,25]
Unknown risk in *males, different histologies/types, genetic profiles*	No studies
Risk TSHD in CAYA cancer survivors (CNS tumor)	**Quality of evidence**
Increased risk after *cranial radiotherapy* vs. no cranial radiotherapy	⊕⊕⊖⊖ LOW [15]
Unknown risk after different doses of cranial radiotherapy, fractionation schedules, types of radiotherapy and spinal radiotherapy	No studies
Unknown risk after *chemotherapy* with or without exposure to radiotherapy	No studies
No significant effect after *neurosurgery* vs. *no neurosurgery*	⊕⊕⊖⊖ LOW [15]
Increased risk in *males* vs. females	⊕⊕⊖⊖ LOW [15]
No significant effect after *hydrocephalus* vs. no hydrocephalus	⊕⊕⊖⊖ LOW [15]

No significant effect of *younger age at tumor diagnosis/treatment* vs. older age	⊕⊕⊖⊖ LOW [15]
No significant effect after *longer follow-up* vs. shorter follow-up	⊕⊕⊖⊖ LOW [15]
Unknown risk for different *ethnicities/races, presence of neurofibromatosis, tumor histologies/types, genetic profiles, ages at follow-up and treatment eras*	No studies
Risk TSHD in CAYA cancer survivors (non-CNS tumor)	**Quality of evidence**
Unknown risk after *radiotherapy to the head and neck region* vs. no radiotherapy	No studies
Increased risk after *higher doses of radiotherapy to the head and neck region* vs. lower doses	⊕⊕⊕⊖ MODERATE [5]
Unknown risk after *total body irradiation*, *different fractionation schedules, types of radiotherapy, spinal radiotherapy, chemotherapy with or without exposure to radiotherapy and brain injury*	No studies
Increased risk in patients with *white ethnicity* vs. non-white ethnicity	⊕⊕⊖⊖ LOW [5]
Increased risk after *younger age at follow-up* vs. older age	⊕⊕⊖⊖ LOW [5]
No significant effect of *longer follow-up* vs. shorter follow-up	⊕⊕⊖⊖ LOW [5]
Unknown risk in *males, histologies/types, genetic profiles and ages at tumor diagnosis/treatment*	No studies
Risk LH/FSHD in CAYA cancer survivors (CNS tumor)	**Quality of evidence**
Increased risk after *cranial radiotherapy* vs. no cranial radiotherapy	⊕⊕⊖⊖ LOW [16]
Unknown risk after different doses of cranial radiotherapy, fractionation schedules, types of radiotherapy and spinal radiotherapy	No studies
Unknown risk after *chemotherapy* with or without exposure to radiotherapy	No studies
Unknown risk after *neurosurgery* vs. no neurosurgery	No studies
Unknown risk in *males, different ethnicities/races, presence of neurofibromatosis, hydrocephalus, different histologies/types, genetic profiles, ages at tumor diagnosis/treatment, ages at follow-up, follow-up durations and treatment eras*	No studies
Risk LH/FSHD in CAYA cancer survivors (non-CNS tumor)	**Quality of evidence**
Unknown risk after *radiotherapy to the head and neck region* vs. no radiotherapy	No studies
Increased risk after *higher doses of radiotherapy to the head and neck region* vs. lower doses	⊕⊕⊕⊖ MODERATE [5]
Unknown risk after *total body irradiation*, *different fractionation schedules, types of radiotherapy, spinal radiotherapy, chemotherapy with or without exposure to radiotherapy and brain injury*	No studies
Increased risk in *males* vs. females	⊕⊕⊖⊖ LOW [5]
Increased risk in patients with *white ethnicity* vs. non-white ethnicity	⊕⊕⊖⊖ LOW [5]
No significant effect of *longer follow-up* vs. shorter follow-up	⊕⊕⊖⊖ LOW [5]
Unknown risk after *different histologies/types, genetic profiles, ages at tumor diagnosis/treatment and ages at follow-up*	No studies
Risk ACTHD in CAYA cancer survivors (CNS tumor)	**Quality of evidence**
Increased risk after *cranial radiotherapy* vs. no cranial radiotherapy	⊕⊕⊕⊖ MODERATE [6,16]
Increased risk after *higher doses of cranial radiotherapy* vs. lower doses	⊕⊕⊖⊖ LOW [21]
Unknown risk after different *fractionation schedules*	No studies

Unknown risk after treatment with different *types of radiotherapy*	No studies
No significant effect of *spinal radiotherapy* vs. no spinal radiotherapy	⊕⊖⊖⊖ VERY LOW [21]
No increased risk of *chemotherapy* vs. no chemotherapy in addition to cranial radiotherapy	⊕⊕⊕⊖ MODERATE [6,16,21]
Unknown risk after *chemotherapy* vs. no chemotherapy, without exposure to radiotherapy	No studies
No significant effect after *neurosurgery* vs. *no neurosurgery*	⊕⊕⊖⊖ LOW [6]
Increased risk in *males* vs. females	⊕⊕⊕⊖ MODERATE [6,16,21]
No significant effect of *younger age at tumor diagnosis/treatment* vs. older age	⊕⊖⊖⊖ VERY LOW [21]
No significant effect after *longer follow-up* vs. shorter follow-up	⊕⊖⊖⊖ VERY LOW [21]
Increased risk in *later treatment era* vs. earlier treatment era	⊕⊕⊖⊖ LOW [6]
Unknown risk for *different ethnicities/races, presence of neurofibromatosis, hydrocephalus, different histologies/types, genetic profiles and ages at follow-up*	No studies
Risk ACTHD in CAYA cancer survivors (non-CNS tumor)	**Quality of evidence**
Unknown risk after *radiotherapy to the head and neck region* vs. no radiotherapy	No studies
Increased risk after *higher doses of radiotherapy to the head and neck region* vs. lower doses	⊕⊕⊖⊖ LOW [5]
Unknown risk after *total body irradiation, different fractionation schedules, types of radiotherapy, spinal radiotherapy, chemotherapy with or without exposure to radiotherapy and brain injury*	No studies
Increased risk after *shorter follow-up* vs. longer follow-up	⊕⊕⊖⊖ LOW [5]
Unknown risk in *males, different ethnicities/races, histologies/types, genetic profiles, ages at tumor diagnosis/treatment and ages at follow-up*	No studies
Risk CPP in CAYA cancer survivors (CNS tumor)	**Quality of evidence**
Increased risk after *cranial radiotherapy* vs. no cranial radiotherapy	⊕⊕⊖⊖ LOW [15]
Unknown risk after different doses of radiotherapy, fractionation schedules, types of radiotherapy and spinal radiotherapy	No studies
No increased risk of *chemotherapy* vs. no chemotherapy in addition to cranial radiotherapy	⊕⊕⊖⊖ LOW [16]
Unknown risk after *chemotherapy* vs. no chemotherapy, without exposure to radiotherapy	No studies
No significant effect after *neurosurgery* vs. *no neurosurgery*	⊕⊕⊖⊖ LOW [15]
Increased risk in *males* vs. females	⊕⊕⊖⊖ LOW [15,16]
Increased risk after *hydrocephalus* vs. no hydrocephalus	⊕⊕⊖⊖ LOW [15]
No significant effect of *younger age at tumor diagnosis/treatment* vs. older age	⊕⊕⊖⊖ LOW [15]
No significant effect after *longer follow-up* vs. shorter follow-up	⊕⊕⊖⊖ LOW [15]
Unknown risk for *different ethnicities/races, presence of neurofibromatosis, histologies/types, genetic profiles, ages at follow-up and treatment eras*	No studies
Risk CPP in childhood cancer survivors (non-CNS tumor)	**Quality of evidence**

Unknown risk after *radiotherapy to the head and neck region, different doses of radiotherapy, total body irradiation, fractionation schedules, types of radiotherapy, spinal radiotherapy, chemotherapy with or without exposure to radiotherapy and brain injury*	No studies
Unknown risk in *males, different ethnicities/races, histologies/types, genetic profiles, ages at tumor diagnosis/treatment, ages at follow-up and follow-up durations*	No studies
2. When should surveillance be initiated? At what frequency and for how long should surveillance be performed?	
Risk GHD in CAYA CNS and non-CNS tumor survivors	**Quality of evidence**
Overall average latency time ranges from <1 to 4.4 years, ranging from minimal 0.05 years to at least 15 years Average latency time *after tumor diagnosis* ranges from 1.4 to 4.4 years, ranging from minimal 0.05 to at least 11.1 years Average latency time *after start radiotherapy* ranges from <1 to 3.96 years, ranging from minimal 0.9 to at least 4.3 years	⊕⊕⊕⊖ MODERATE [15,17-19,26,30-35]
Shorter latency time after *higher doses of radiotherapy* vs. lower doses	⊕⊕⊖⊖ LOW [18,19]
Cumulative incidence increases over time which does not seem to plateau	⊕⊕⊕⊖ MODERATE [5,6,15,16,18,19,26,33,35,37,38]
Modifying factors of cumulative incidence unknown	No studies
Risk TSHD in CAYA CNS and non-CNS tumor survivors	**Quality of evidence**
Overall average latency time ranges from 1.8 to 5.1 years, ranging from minimal 0.02 years to at least 11.9 years Average latency time *after tumor diagnosis* ranges from 2.8 to 4.5 years, ranging from minimal 0.02 to at least 11.9 years	⊕⊕⊖⊖ LOW [15,31,33,36]
Modifying factors of latency time unknown	No studies
Cumulative incidence increases over time; presence of plateau can not be assessed	⊕⊕⊖⊖ LOW [5,15,16,33,36]
Modifying factors of cumulative incidence unknown	No studies
Risk LH/FSHD in CAYA CNS and non-CNS tumor survivors	**Quality of evidence**
Average latency time *after tumor diagnosis* ranges from 4.5 to 10.2 years, ranging from minimal 0.2 to at least 11.6 years	⊕⊖⊖⊖ VERY LOW [15,31]
Modifying factors of latency time unknown	No studies
Cumulative incidence increases over time; presence of plateau can not be assessed	⊕⊕⊖⊖ LOW [5,15,16]
Modifying factors of cumulative incidence unknown	No studies
Risk ACTHD in CAYA CNS and non-CNS tumor survivors	**Quality of evidence**
Overall average latency time ranges from 2.5 to 7.0 years, ranging from minimal 0.01 to at least 8.7 years Average latency time *after tumor diagnosis* ranges from 2.5 to 6.6 years, ranging from minimal 0.01 to at least 8.7 years Average latency time *after the end of treatment* ranges from 2.9 to 7.0 years, ranging from minimal 0.75 to at least 7.5 years	⊕⊕⊖⊖ LOW [15,17,31,35,36]
Modifying factors of latency time unknown	No studies

Cumulative incidence increases over time; presence of plateau can not be assessed	⊕⊕⊖⊖ LOW [5,6,15,16,33,35-38]
Modifying factors of cumulative incidence unknown	No studies
Risk CPP in childhood CNS and non-CNS tumor survivors	**Quality of evidence**
Average latency time *after tumor diagnosis* ranges from 3.1 to 3.8 years, ranging from minimal 0.1 to at least 8.8 years	⊕⊕⊖⊖ LOW [15,31]
Modifying factors of latency time unknown	No studies
Cumulative incidence increases over time; plateau is not applicable	⊕⊕⊖⊖ LOW [15,16,37]
Modifying factors of cumulative incidence unknown	No studies
Order of occurrence of HP dysfunction in general	**Quality of evidence**
Order of occurrence HP dysfunction CAYA CNS and non-CNS tumor survivors	See Figure 2
Order of occurrence of HP dysfunction in CAYA CNS tumor survivors with a tumor in the sellar and suprasellar region versus brain tumors elsewhere in the brain unknown	No studies
Order of occurrence HP dysfunction in CAYA non-CNS tumor survivors after brain injury unknown	No studies
3. What surveillance modality should be used?	
Diagnostic value of testing modalities to detect GHD in CAYA CNS and non-CNS tumor survivors	**Quality of evidence**
Diagnostic value of IGF-1 compared to GH dynamic testing to detect GHD in cancer survivors of pediatric age is moderate (sensitivity ranged from 47% to 80%, specificity ranged from 77% to 100%)	⊕⊖⊖⊖ VERY LOW [39-42]
Diagnostic value IGFBP-3 compared to GH dynamic testing to detect GHD in cancer survivors of pediatric age is moderate (sensitivity is 20%, specificity is 100%, AUC 0.617)	⊕⊖⊖⊖ VERY LOW [39,40,42]
Unknown diagnostic value of height plotted in a growth chart compared to GH dynamic testing in cancer survivors of pediatric age	No studies
Unknown diagnostic value IGF-1 or IGFBP-3 to detect GHD in adult cancer survivors	No studies
Diagnostic value of testing modalities to detect TSHD in CAYA CNS and non-CNS tumor survivors	**Quality of evidence**
Correlation between nocturnal TSH surge and FT4 concentrations to detect TSHD is low	⊕⊖⊖⊖ VERY LOW [43,44]
Correlation between TSH peak after TRH test and FT4 concentrations to detect TSHD is low	⊕⊖⊖⊖ VERY LOW [43,44]
Correlation between TSH decline after TRH test and FT4 concentrations to detect TSHD is low	⊕⊖⊖⊖ VERY LOW [43,44]
Diagnostic value of testing modalities to detect LH/FSHD in CAYA CNS and non-CNS tumor survivors	**Quality of evidence**
Unknown diagnostic value of Tanner stage, bone age, LH, FSH and sex steroids measurements to detect LH/FSHD	No studies
Unknown interobserver variability and likelihood performance for defining Tanner stages among health care providers from different specialities	No studies

Diagnostic value of testing modalities to detect ACTHD in CAYA CNS and non-CNS tumor survivors	**Quality of evidence**
The agreement between morning cortisol and low dose-ACTH test to detect ACTHD in cancer survivors of pediatric age is poor (Agreement 63%, kappa 0.25)	⊕⊖⊖⊖ VERY LOW [45]
Diagnostic value of morning plasma cortisol versus dynamic testing (preferably ITT) for detecting ACTHD in adult cancer survivors	Existing guidelines
Influence of steroid use on the testing results of the corticotropic axis	No studies
Confounders which bias the testing results of the corticotropic axis	Expert opinion
Diagnostic value of testing modalities to detect CPP in childhood CNS and non-CNS tumor survivors	**Quality of evidence**
Unknown diagnostic value of Tanner stage and/or growth velocity compared to LH, FSH, sex steroids, LHRH/GnRH testing, pelvic ultrasound and/or bone age	No studies
Unkown diagnostic value of testes volume in boys treated with gonadotoxic therapy	No studies
4. What should be done when abnormalities are identified?	
Potential harms of treatment of HP dysfunction in CAYA cancer survivors	**Quality of evidence**
Suggestion for possible significant effect of GH therapy on the occurrence of secondary neoplasms	⊕⊖⊖⊖ VERY LOW [53-60]
No significant effect of GH therapy on the occurrence of tumor recurrence	⊕⊕⊕⊖ MODERATE [53,56,57,59,62-65]
Potential benefits of treatment of HP dysfunction in CAYA cancer survivors	**Quality of evidence**
Improvement of final height, bone mineral density and cardiovascular and metabolic health after treatment of GHD	Expert opinion, existing guidelines[47,48,66-69]
Improvement of final height, metabolic health and quality of life (including fatigue) after treatment of TSHD	Expert opinion, existing guidelines[48,51]
Adequate pubertal development and maintenance of secondary sex characteristics, fertility, bone mineral density, final height, psychological well-being (including sexual health) / quality of life after treatment of LH/FSHD	Expert opinion, existing guidelines[48,52,70]
Prevention of adrenal crisis, and possibly mortality, improvement of fatigue and quality of life after treatment of ACTHD	Expert opinion, existing guidelines[48]
Improvement of final height and psychological well-being/quality of life after treatment of CPP	Expert opinion, existing guidelines[71]

When should surveillance for HP dysfunction be initiated?

Evidence for time of onset of HP dysfunction

The overall average time to presentation with HP dysfunction after diagnosis or treatment ranges from <1 to 4.4 years (range, 0.05-15) for GHD[15,17-19,26,30-35] (moderate quality evidence), 1.8 to 5.1 years (range, 0.02-11.9) for TSHD[15,31,33,36] (low quality evidence), 4.5 to 10.2 years (range, 0.2-11.6) for LH/FSHD[15,31] (very low quality evidence), 2.5 to 7.0 years (range, 0.01-8.7) for ACTHD[15,17,31,35,36] (low quality evidence), and 3.1 to 3.8 years (range, 0.1-8.8) for CPP [15,31](low quality evidence). Shorter latency times were observed for GHD[18,19] after higher RT doses compared to lower RT doses (low quality evidence). For other types of HP dysfunction (i.e. TSHD, LH/FSHD, ACTHD, and CPP), studies that assessed factors influencing latency times were not identified. Latency times of different types of HP dysfunction reveal that GHD generally occurs first, followed by TSHD, ACTHD and LH/FSHD (Figure 2). In general, if one HP axis is distorted, the risk for dysfunction of other HP axes increases.

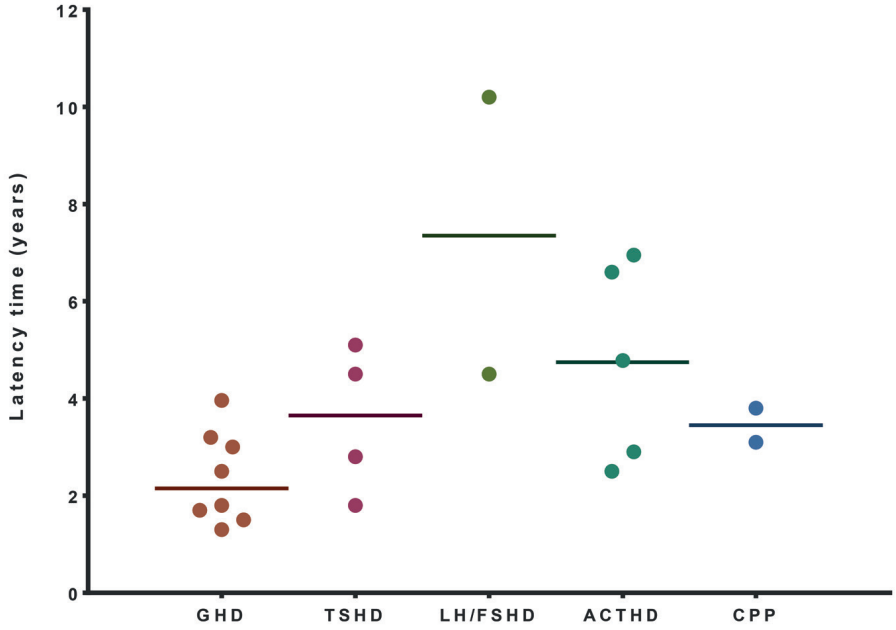
Considerations of evidence that led to decision making regarding recommendations

There is discordance among existing guidelines about the timing of initiation of surveillance for HP dysfunction. CAYA cancer survivors with CNS tumors or surgery near or within the HP region, or with a history of hydrocephalus (GHD and CPP) are particularly prone to the development of HP dysfunction from diagnosis or surgery. In CAYA cancer survivors exposed to RT, surveillance for HP dysfunction may be initiated after 1 year from start RT, as linear growth and thyroid function may be affected by treatment exposures and malnutrition during the first year. However, monitoring height and pubertal status at six months after RT is desirable, as interpretation of growth and pubertal development requires multiple measurements over time. Oncology and primary care clinicians involved in the follow-up care of CAYA cancer survivors should be aware that HP dysfunction may already present in the first year after RT exposure.

Recommendations for initiation of surveillance

Initiation of surveillance for HP dysfunction is recommended at ≥1 year from start RT, or from diagnosis or surgery in CAYA survivors with CNS tumors or surgery near or within the HP region, or from occurrence of hydrocephalus (GHD and CPP) (moderate (GHD), low (TSHD, ACTHD, CPP) or very low (LH/FSHD) quality evidence and expert opinion, strong recommendation).

Figure 2. Latency times of HP dysfunction



At what frequency should surveillance for HP dysfunction be performed?

Evidence for cumulative incidence of HP dysfunction

There is moderate (GHD[5,6,15,16,18,19,26,33,35,37,38]) and low (TSHD[5,15,16,33,36], LH/FSHD[5,15,16], ACTHD[5,6,15,16,33,35-38], CPP[15,16,37]) quality evidence that the cumulative incidence of HP dysfunction increases over time. The predictors for change of the risk of HP dysfunction over time are unknown. For GHD[5,6,15,16,18,19,26,33,35,37,38], there is moderate quality evidence that the cumulative incidence does not seem to plateau. For TSHD, LH/FSHD and ACTHD, the presence of a plateau could not be assessed, and for CPP a plateau is not applicable due to the fact that CPP can only be diagnosed in girls < 8 years of age and boys < 9 years of age.

Considerations of evidence that led to decision making regarding recommendations

Defining the appropriate surveillance time interval for testing is difficult due to lack of evidence. Discordance among the existing guidelines relate to the frequency surveillance for HP dysfunction, which is also dependent on the type of screening modality. The expert panel recommends surveillance with physical examination, including monitoring of height and pubertal status every 6 months in pre- and peri-pubertal cancer survivors as benefits of timely intervention outweigh the harms of frequent screening. Laboratory measurements in pre- and

peri-pubertal cancer survivors should be obtained annually. The experts also agree that annual surveillance for HP dysfunction in post-pubertal survivors is appropriate.

Recommendations for frequency of follow-up

Monitoring of height (GHD, TSHD, LH/FSHD and CPP) and pubertal status (GHD, LH/FSHD and CPP) is recommended every 6 months for at-risk pre- or peri-pubertal cancer survivors (expert opinion, strong recommendation). Annual surveillance with laboratory measurements (TSHD and ACTHD) is recommended in pre- or peri-pubertal at-risk cancer survivors (expert opinion, strong recommendation). In post-pubertal at-risk cancer survivors, annual surveillance for HP dysfunction is recommended (moderate (GHD) and low (TSHD, LH/FSHD and ACTHD) quality evidence and expert opinion, strong recommendation).

For how long should surveillance for HP dysfunction be performed?

Evidence for plateau in occurrence of HP dysfunction

The cumulative incidence of GHD (moderate quality evidence), TSHD, LH/FSHD, ACTHD and CPP (low quality evidence) increases over time. For GHD the cumulative incidence does not seem to plateau, but for TSHD, LH/FSHD and ACTHD this could not be assessed due to lack of data.

Considerations of evidence that led to decision making regarding recommendations

Studies addressing latency times and cumulative incidences for HP dysfunction concerned mainly studies with prospective evaluation, but generally short follow-up durations, or retrospective studies with longer follow-up durations. In the identified studies, screening occurred at variable times from treatment. This may have resulted in delayed diagnosis of occult HP dysfunction resulting in underestimation of lower limits and overestimation of upper limits of reported latency times. There is a dearth of studies with longitudinal and systematic surveillance of HP dysfunction for longer follow-up durations resulting in discordance among existing guidelines about the duration for surveillance of HP dysfunction. The expert panel assessed that HP dysfunction may occur many years after treatment and that in light of the limitations of available evidence, no recommendations can be formulated regarding when HP function surveillance should be stopped.

Recommendations for duration of follow-up

Surveillance for HP dysfunction is reasonable for at-risk CAYA cancer survivors for at least 15 years from RT exposure or after diagnosis (low quality evidence and expert opinion, moderate recommendation). Data pertaining to the risk for new onset HP dysfunction 15 years after diagnosis and treatment of CAYA survivors, are lacking. Monitoring past this point should be

tailored to each individual and guided by patient and provider preferences, taking into account available local resources.

What surveillance modality should be used?

Evidence for surveillance modalities for HP dysfunction

Existing guidelines for surveillance of HP dysfunction were concordant on measuring height and pubertal staging to screen for HP dysfunction. Very low quality evidence shows a moderate diagnostic value of insulin-like growth factor 1 (IGF-1) or insulin-like growth factor-binding protein 3 (IGFBP-3) to detect GHD[39-41] in childhood cancer survivors, in line with a recent systematic review[42]. We did not identify studies regarding the diagnostic value of height plotted on a growth chart, versus dynamic GH testing in cancer survivors of pediatric age. In addition, no studies were identified with our selection criteria that evaluated the diagnostic value of IGF-1 and IGFBP-3 to detect GHD in adult cancer survivors. Two studies assessed the value of dynamic thyrotropin releasing hormone (TRH) testing and nocturnal TSH surge to detect TSHD[43,44]. One study demonstrated no correlation between dynamic TRH testing (i.e. TSH peak or TSH decline) or nocturnal TSH surge, and FT4 concentrations (very low quality evidence).[44] The second study assessed similar testing modalities for TSHD, but without clear distinction between the index and reference test, which made it impossible to report testing characteristics.[43] Very low quality evidence demonstrates a poor agreement between morning cortisol and low dose ACTH test to detect ACTHD[45] in survivors of pediatric age. No studies were identified regarding the diagnostic value of Tanner staging, bone age, LH, FSH, sex steroid measurements, and dynamic testing to detect LH/FSHD or CPP in CAYA cancer survivors.

Considerations of evidence that led to decision making regarding recommendations

Experts considered the established methods of screenings modalities for HP dysfunction in the general pediatric and adult populations.

Screening for GHD in children includes height standard deviation scores (SDS) plotted in a growth chart, declining growth or failure of acceleration of growth velocity in combination with advancing Tanner stage and clinical history and auxology suggesting GHD.[46,47] Although IGF-1 and IGFBP-3 have high specificity to detect GHD in cancer survivors of pediatric age, their sensitivity is low, potentially leading to a high percentage of survivors with undetected GHD. In addition, these measurements require blood withdrawal and correct interpretation in the clinical context. The experts believe that IGF-1 or IGFBP-3 do not provide added value to growth measurements in detecting GHD in pre- and peri-pubertal cancer survivors, assuming that Tanner stage is always evaluated when interpreting growth velocity.

In adults, the Endocrine Society guidelines recommend provocative testing if GHD is suspected.[48] In childhood cancer survivors exposed to RT including the HP axis, guidelines advise against relying solely on serum IGF-1 levels to make the diagnosis of GHD.[46] In adults, a normal IGF-1 level does not exclude the diagnosis of GHD, but makes provocative testing mandatory for the diagnosis of GHD.[49] However, low IGF-1 levels, in the absence of catabolic conditions such as poorly controlled diabetes, liver disease, and oral estrogen therapy, are seen as strong evidence for significant GHD and may be useful in identifying patients who may benefit from treatment and therefore require GH stimulation testing. The experts agree that although an IGF-1 level >0 SDS does not rule out GHD in post-pubertal CAYA cancer survivors, it makes the diagnosis GHD very unlikely, especially in absence of clinical symptoms. An IGF-1 level <0 SDS together with clinical symptoms is suggestive for GHD, and requires referral to an endocrinologist, although pitfalls in the interpretation of IGF-1 levels should be considered.[50]

Established methods to screen and diagnose TSHD, as recommended by the Endocrine Society and European Thyroid Association, include assessment of FT4 and TSH levels in both children and adults.[48,51] There may be difficulties with the interpretation of thyroid laboratory results, as central and primary damage may overlap, especially when both the pituitary and thyroid gland have been exposed to RT.

Established screening methods for ACTHD in adults as recommended by the Endocrine Society include morning serum cortisol levels.[48] In children, no guidelines exist about the optimal screening modality for ACTHD. The diagnostic value of morning cortisol is low, but clinical symptoms for ACTHD are nonspecific. The experts believe that measurements of morning cortisol in both children and adults are reasonable to screen for ACTHD.

For surveillance of LH/FSHD in cancer survivors, the Endocrine Society guidelines recommend similar screening strategies as for the general population, which includes Tanner staging in pre- and peri-pubertal cancer survivors[46]. In CAYA cancer survivors past the age of 13 years (females) or 14 years (males) with signs and symptoms suggesting LH/FSHD, serum testosterone and LH (in males) and estradiol and FSH (in females) may be measured to distinguish central from primary forms of hypogonadism.[48,52] There may be difficulties with the interpretation of laboratory results for hypogonadism, as central and primary damage may overlap, especially when both the pituitary and testes/ovaries have been exposed to toxic therapies. Screening for CPP includes Tanner staging for both boys and girls, although testicular volumes may not be reliable in boys treated with gonadotoxic agents.[46] For surveillance of CPP and LH/FSHD in pre- or peri-pubertal cancer survivors, physical examination can be reliably used to establish both diagnoses.

Recommendations for surveillance modalities

Providers should take a relevant clinical history and perform a physical examination for signs and symptoms of HP dysfunction in all at-risk CAYA cancer survivors. History and physical examination should assess complaints, signs and symptoms suggestive of abnormal growth or pubertal development, hypogonadism, hypothyroidism and adrenal insufficiency (existing guidelines and expert opinion, strong recommendation). Monitoring of growth velocity (height, expressed as standard deviation and plotted in a growth chart) in relation to parental height (GHD, TSHD, LH/FSHD and CPP), pubertal development and pubertal progression (Tanner stage) are recommended (GHD, LH/FSHD and CPP) for at-risk pre- and peri-pubertal cancer survivors (high quality evidence and expert opinion, strong recommendation). For post-pubertal cancer survivors, it is reasonable to screen for GHD with IGF-1 measurements and clinical symptoms, with the understanding that a normal IGF-1 level does not rule out the diagnosis of GHD (expert opinion, moderate recommendation). Laboratory measurements, including FT4 and TSH (to detect TSHD), and morning cortisol (to detect ACTHD), are recommended in at-risk CAYA cancer survivors (existing guidelines and expert opinion, strong recommendation). Measurements of total testosterone concentration in an early morning blood sample, and LH are recommended in at-risk male CAYA cancer survivors with clinical signs and past the age of 14 years (expert opinion, strong recommendation). Screening with estradiol and FSH are recommended for evaluation of LH/FSHD in at-risk female CAYA cancer survivors past the age of 13 years who present with clinical signs suggesting LH/FSHD (expert opinion, strong recommendation).

What should be done when abnormalities are identified?

Evidence for benefits and harms of treatment for HP dysfunction

In our systematic literature review we did not identify randomized controlled trials that assessed the benefits and harms of hormone replacement therapy in CAYA cancer survivors.

Potential harms

GH therapy has been implicated in the occurrence of secondary neoplasms in CAYA cancer survivors (very low quality evidence).[53-60] However, a recent meta-analysis reported no significant difference in the occurrence of secondary tumors among GH treated vs. GH untreated survivors of childhood cancer[61]. Moderate quality evidence demonstrated no association between GH therapy and tumor recurrence in CAYA cancer survivors.[53,56,57,59,62-65]

Potential benefits

Potential benefits of hormone replacement therapy include improvement of final height, bone mineral density and cardiovascular and metabolic health for GHD[47,48,66-69]; improvement of final height, metabolic health and quality of life (including fatigue) for TSHD[48,51]; adequate pubertal

development and maintenance of secondary sex characteristics, fertility, bone mineral density, final height, psychological well-being (including sexual health)/quality of life for LH/FSHD[48,52,70]; prevention of adrenal crisis, and possibly mortality, improvement of fatigue and quality of life for ACTHD[48]; and improved final height and psychological well-being/quality of life for CPP[71].

Considerations of evidence that led to decision making regarding recommendations

The experts agree that, overall the benefits of hormone replacement outweigh the harms of untreated HP dysfunction. There is lack of data regarding the optimal timing to initiate GH treatment after achieving complete remission of cancer, or in case of stable residual disease. The experts believe timing and initiation of GH therapy in CAYA cancer survivors should be carefully determined by a multidisciplinary team. GH treatment should only be initiated after counselling the patient and parents on its benefits and possible harms.

Recommendations for counselling and referral

Referral to a pediatric endocrinologist is recommended for pre- and peri-pubertal cancer survivors experiencing decline in growth velocity suggestive for GHD and that is unexpected for their age and/or height SDS below the target height range SDS, and can not be explained by other causes (expert opinion, strong recommendation). Referral is recommended, as appropriate, to a pediatric or adult endocrinology provider in the presence of clinical symptoms, or laboratory results suggestive for HP dysfunction (expert opinion, strong recommendation). CAYA cancer survivors should be counseled regarding the benefits of hormonal replacement on overall health, as well as the risks associated with untreated hormonal deficits, and should be assisted in coordinating and obtaining an early referral when appropriate (expert opinion, strong recommendation).

Conclusion

The harmonized surveillance recommendations for HP dysfunction are based on a transparent process and are intended to improve health outcomes following HP dysfunction by facilitating consistent long-term follow-up care in CAYA cancer survivors. Identified data that informed this guideline underscore the paucity of high-quality evidence and need for further targeted research.

Table 3. Harmonized recommendations for HP dysfunction surveillance for childhood, adolescent and young adult cancer survivors

General recommendation
Childhood, adolescent and young adult cancer survivors treated with radiotherapy exposing the HP region (high quality evidence), or with CNS tumors (high quality evidence and expert opinion) or surgery near or within the HP region (expert opinion), or with a history of hydrocephalus or cerebrospinal fluid shunt (low quality evidence and expert opinion), and their health-care providers, should be aware of the risk of HP dysfunction (strong recommendation).

GHD

Who needs surveillance for GHD?
Surveillance for GHD is recommended for childhood, adolescent and young adult (CAYA) cancer survivors: · Treated with radiotherapy exposing the HP region (high quality evidence) · CNS tumor near or within the HP region (high quality evidence and expert opinion) · Surgery near or within the HP region (expert opinion) (strong recommendation).
Surveillance for GHD is reasonable for CAYA cancer survivors with a history of hydrocephalus or cerebrospinal fluid shunt (low quality evidence and expert opinion, moderate recommendation).
Surveillance for GHD is reasonable for CAYA cancer survivors treated with TBI (very low quality evidence, moderate recommendation).
When should surveillance for GHD be initiated?
Initiation of surveillance for GHD is recommended · at ≥1 year from start radiotherapy even in the absence of symptoms‡ · or from diagnosis in CAYA cancer survivors with CNS tumors or surgery near or within the HP region, or from occurrence of hydrocephalus or cerebrospinal fluid shunt (moderate quality evidence and expert opinion, strong recommendation).
At what frequency should surveillance for GHD be performed?
Monitoring of height and pubertal status is recommended every 6 months for at-risk pre- and peri-pubertal cancer survivors* (expert opinion, strong recommendation).
Annual surveillance for GHD is recommended for at-risk post-pubertal CAYA cancer survivors* (moderate quality evidence and expert opinion, strong recommendation).
For how long should surveillance for GHD be performed?
Surveillance for GHD is reasonable for at-risk CAYA cancer survivors* for at least 15 years from radiotherapy exposure or after diagnosis (low quality evidence and expert opinion, moderate recommendation).
What surveillance modality should be used for GHD?
Providers should take a relevant clinical history and perform a physical examination in at-risk CAYA cancer survivors*. History and physical examination should capture complaints, signs and symptoms suggestive of GHD (existing guidelines and expert opinion, strong recommendation).
Monitoring of growth velocity (height, expressed as standard deviation and plotted in a growth chart) in relation to parental height, pubertal development and pubertal progression (Tanner stage) are recommended for pre- and peri-pubertal at-risk cancer survivors* (high quality evidence and expert opinion, strong recommendation).

For post-pubertal at-risk CAYA cancer survivors*, it is reasonable to screen for GHD with IGF-1 measurements and clinical symptoms, with the understanding that a normal IGF-1 level does not rule out the diagnosis of GHD (expert opinion, moderate recommendation).
What should be done when abnormalities are identified?
Referral to a pediatric endocrinologist is recommended for pre- and peri-pubertal cancer survivors experiencing decline in growth velocity suggestive for GHD and that is unexpected for their age and/or height SDS below the target height range SDS, and can not be explained by other causes (expert opinion, strong recommendation).
Referral to an endocrinologist is recommended for post-pubertal CAYA cancer survivors with clinical symptoms or laboratory results suggestive for GHD (expert opinion, strong recommendation).
CAYA cancer survivors with (a suspicion for) GHD should be counseled regarding the benefits of hormonal replacement therapy for GHD on overall health, as well as the risks associated with untreated GHD, and should be assisted in coordinating and obtaining an early referral when appropriate (expert opinion, strong recommendation).

*At-risk CAYA survivors include survivors treated with radiotherapy exposing the HP region, with CNS tumors or surgery near or within the HP region, or with a history of hydrocephalus or cerebrospinal fluid shunt.

‡ Monitoring height and pubertal status at six months after RT is desirable, as interpretation of growth and pubertal development requires multiple measurements over time. Oncology and primary care clinicians involved in the follow-up care of CAYA cancer survivors should be aware that GHD may already present in the first year after RT exposure.

TSHD

Who needs surveillance for TSHD?
Surveillance for TSHD is recommended for childhood, adolescent and young adult (CAYA) cancer survivors: · Treated with radiotherapy exposing the HP region (low quality evidence and expert opinion) · CNS tumor near or within the HP region (high quality evidence and expert opinion) · Surgery near or within the HP region (expert opinion) (strong recommendation).
When should surveillance for TSHD be initiated?
Initiation of surveillance for TSHD is recommended · at ≥1 year from start radiotherapy even in the absence of symptoms‡ · or from diagnosis in CAYA cancer survivors with CNS tumors or surgery near or within the HP region (low quality evidence and expert opinion, strong recommendation).
At what frequency should surveillance for TSHD be performed?
Monitoring of height every 6 months, and annual laboratory measurements are recommended for at-risk pre- and peri-pubertal cancer survivors* (expert opinion, strong recommendation).
Annual surveillance for TSHD is recommended for at-risk post-pubertal CAYA cancer survivors* (low quality evidence and expert opinion, strong recommendation).
For how long should surveillance for TSHD be performed?
Surveillance for TSHD is reasonable for at-risk CAYA cancer survivors* for at least 15 years from radiotherapy exposure or after diagnosis (low quality evidence and expert opinion, moderate recommendation).
What surveillance modality should be used for TSHD?

Providers should take a relevant clinical history and perform a physical examination in at-risk CAYA cancer survivors*. History and physical examination should capture complaints, signs and symptoms suggestive of TSHD (existing guidelines and expert opinion, strong recommendation).
Monitoring of growth velocity (height, expressed as standard deviation and plotted in a growth chart) in relation to parental height, pubertal development and pubertal progression are recommended for pre- and peri-pubertal at-risk cancer survivors* (high quality evidence and expert opinion, strong recommendation).
Laboratory measurements, including FT4 and TSH are recommended in at-risk CAYA cancer survivors* (existing guidelines and expert opinion, strong recommendation).
What should be done when abnormalities are identified?
Referral to an (pediatric) endocrinologist is recommended for CAYA cancer survivors with clinical symptoms or laboratory results suggestive for TSHD (expert opinion, strong recommendation).
CAYA cancer survivors with (a suspicion for) TSHD should be counseled regarding the benefits of hormonal replacement for TSHD on overall health, as well as the risks associated with untreated TSHD, and should be assisted in coordinating and obtaining an early referral when appropriate (expert opinion, strong recommendation).

*At-risk CAYA survivors include survivors treated with radiotherapy exposing the HP region, or with CNS tumors or surgery near or within the HP region.
‡Monitoring height at six months after RT is desirable, as interpretation of growth requires multiple measurements over time. Oncology and primary care clinicians involved in the follow-up care of CAYA cancer survivors should be aware that TSHD may already present in the first year after RT exposure.

LH/FSHD

Who needs surveillance for LH/FSHD?
Surveillance for LH/FSHD is recommended for childhood, adolescent and young adult (CAYA) cancer survivors: · Treated with radiotherapy exposing the HP region (low quality evidence and expert opinion) · CNS tumor near or within the HP region (high quality evidence and expert opinion) · Surgery near or within the HP region (expert opinion) (strong recommendation).
When should surveillance for LH/FSHD be initiated?
Initiation of surveillance for LH/FSHD is recommended† · at ≥1 year from start radiotherapy even in the absence of symptoms‡ · or from diagnosis in survivors with CNS tumors or surgery near or within the HP region (very low quality evidence and expert opinion, strong recommendation).
At what frequency should surveillance for LH/FSHD be performed?
Monitoring of height and pubertal status is recommended every 6 months for at-risk pre- and peri-pubertal cancer survivors* (expert opinion, strong recommendation).
Annual surveillance for LH/FSHD is recommended for at-risk post-pubertal CAYA cancer survivors* (low quality evidence and expert opinion, strong recommendation).
For how long should surveillance for LH/FSHD be performed?
Surveillance for LH/FSHD is reasonable for at-risk CAYA cancer survivors* for at least 15 years from radiotherapy exposure or after diagnosis (low quality evidence and expert opinion, moderate recommendation).

What surveillance modality should be used for LH/FSHD?
Providers should take a relevant clinical history and perform a physical examination in at-risk CAYA survivors*. History and physical examination should capture complaints, signs and symptoms suggestive of LH/FSHD (existing guidelines and expert opinion, strong recommendation).
Monitoring of growth velocity (height, expressed as standard deviation and plotted in a growth chart) in relation to parental height, pubertal development and pubertal progression (Tanner stage) are recommended for pre- and peri-pubertal at-risk cancer survivors* (high quality evidence and expert opinion, strong recommendation).
Laboratory measurements, including morning testosterone and LH (in males) or estradiol and FSH (in females) are recommended in at-risk CAYA cancer survivors* past 13 years (females) or 14 years (males) with clinical signs (existing guidelines and expert opinion, strong recommendation).
What should be done when abnormalities are identified?
Referral to an (pediatric) endocrinologist is recommended for CAYA cancer survivors with clinical signs and symptoms suggestive for LH/FSHD (expert opinion, strong recommendation).
CAYA cancer survivors with (a suspicion for) LH/FSHD should be counseled regarding the benefits of hormonal replacement for LH/FSHD on overall health, as well as the risks associated with untreated LH/FSHD, and should be assisted in coordinating and obtaining an early referral when appropriate (expert opinion, strong recommendation).

*At-risk CAYA survivors include survivors treated with radiotherapy exposing the HP region, or with CNS tumors or surgery near or within the HP region.
† Surveillance should be started by no later than 13 years (and no earlier than 10 years) in boys, and no later than 12 years (and no earlier than 9 years) in girls
‡ Monitoring height and pubertal status at six months after RT is desirable, as interpretation of growth and pubertal development requires multiple measurements over time. Oncology and primary care clinicians involved in the follow-up care of CAYA cancer survivors should be aware that LH/FSHD may already present in the first year after RT exposure.

ACTHD

Who needs surveillance for ACTHD?
Surveillance for ACTHD is recommended for childhood, adolescent and young adult (CAYA) cancer survivors: · Treated with radiotherapy exposing the HP region (moderate quality evidence) · CNS tumor near or within the HP region (high quality evidence and expert opinion) · Surgery near or within the HP region (expert opinion) (strong recommendation).
When should surveillance for ACTHD be initiated?
Initiation of surveillance for ACTHD is recommended · at ≥1 year from start radiotherapy even in the absence of symptoms · or from diagnosis in CAYA cancer survivors with CNS tumors or surgery near or within the HP region (low quality evidence and expert opinion, strong recommendation).
At what frequency should surveillance for ACTHD be performed?
Annual surveillance for ACTHD is recommended for at-risk CAYA cancer survivors* (low quality evidence and expert opinion, strong recommendation).
For how long should surveillance for ACTHD be performed?

Surveillance for ACTHD is reasonable for at-risk CAYA cancer survivors* for at least 15 years from exposure to RT or after diagnosis (low quality evidence and expert opinion, moderate recommendation).
What surveillance modality should be used for ACTHD?
Providers should take a relevant clinical history and perform a physical examination in at-risk CAYA cancer survivors*. History and physical examination should capture complaints, signs and symptoms suggestive of ACTHD (existing guidelines and expert opinion, strong recommendation).
Laboratory measurements, including morning cortisol are recommended in at-risk CAYA cancer survivors* (existing guidelines and expert opinion, strong recommendation).
What should be done when abnormalities are identified?
Direct referral to an (pediatric) endocrinologist is recommended for CAYA cancer survivors with low morning cortisol (expert opinion, strong recommendation).
CAYA cancer survivors with (a suspicion for) ACTHD should be counseled regarding the benefits of hormonal replacement for ACTHD on overall health, as well as the risks associated with untreated ACTHD, and should be assisted in coordinating and obtaining an early referral when appropriate. (expert opinion, strong recommendation).

*At-risk CAYA survivors include survivors treated with radiotherapy exposing the HP region, or with CNS tumors or surgery near or within the HP region.

CPP

Who needs surveillance for CPP?
Surveillance for CPP is recommended for childhood cancer survivors below age 8 years (girls) or 9 years (boys): · Treated with radiotherapy exposing the HP region (low quality evidence and expert opinion) · CNS tumor near or within the HP region (high quality evidence and expert opinion) · Surgery near or within the HP region (expert opinion). · History of hydrocephalus or cerebrospinal fluid shunt (low quality evidence and expert opinion) (strong recommendation).
When should surveillance for CPP be initiated?
Initiation of surveillance for CPP is recommended · from diagnosis in childhood cancer survivors with CNS tumors or surgery near or within the HP region, or from occurrence of hydrocephalus or cerebrospinal fluid shunt · or at ≥1 year from start radiotherapy even in the absence of symptoms‡ (low quality evidence and expert opinion, strong recommendation).
At what frequency should surveillance for CPP be performed?
Monitoring of height and pubertal status is recommended every 6 months for at-risk childhood cancer survivors* (expert opinion, strong recommendation).
For how long should surveillance for CPP be performed?
Surveillance for CPP is recommended for at-risk childhood cancer survivors until age 8 years in girls and 9 years in boys (low quality evidence and expert opinion, strong recommendation).
What surveillance modality should be used?
Providers should take a relevant clinical history and perform a physical examination in at-risk childhood cancer survivors*. History and physical examination should capture signs and symptoms suggestive of CPP (existing guidelines and expert opinion, strong recommendation).

Monitoring of growth velocity (height, expressed as standard deviation and plotted in a growth chart) in relation to parental height, pubertal development and pubertal progression (Tanner stage) are recommended for pre- and peri-pubertal at-risk cancer survivors* (high quality evidence and expert opinion, strong recommendation).
What should be done when abnormalities are identified?
Referral to a pediatric endocrinologist is recommended for childhood cancer survivors with clinical signs and symptoms suggestive for CPP (expert opinion, strong recommendation)
Cancer survivors with (a suspicion for) CPP should be counseled regarding the benefits of treatment for CPP on overall health as well as the risks associated with untreated CPP, and should be assisted in coordinating and obtaining an early referral when appropriate (expert opinion, strong recommendation).

*At-risk childhood cancer survivors include survivors treated with radiotherapy exposing the HP region, with CNS tumors or surgery near or within the HP region, or with a history of hydrocephalus or cerebrospinal fluid shunt.

‡ Monitoring height and pubertal status at six months after RT is desirable, as interpretation of growth and pubertal development requires multiple measurements over time. Oncology and primary care clinicians involved in the follow-up care of CAYA cancer survivors should be aware that CPP may already present in the first year after RT exposure, necessitating early referral.

References

1. Gatta G, Zigon G, Capocaccia R, et al. Survival of European children and young adults with cancer diagnosed 1995-2002. *Eur J Cancer.* 2009;45(6):992-1005.
2. Howlader N NA, Krapcho M, Miller D, et al (eds). SEER Cancer Statistics Review, 1975–2013. National Cancer Institute: Bethesda, MD, 2016. http://seer.cancer.gov/csr/1975_2013 (accessed February 4, 2019).
3. Robison LL, Hudson MM. Survivors of childhood and adolescent cancer: life-long risks and responsibilities. *Nat Rev Cancer.* 2014;14(1):61-70.
4. Mostoufi-Moab S, Seidel K, Leisenring WM, et al. Endocrine Abnormalities in Aging Survivors of Childhood Cancer: A Report From the Childhood Cancer Survivor Study. *J Clin Oncol.* 2016;34(27):3240-3247.
5. Chemaitilly W, Li Z, Huang S, et al. Anterior hypopituitarism in adult survivors of childhood cancers treated with cranial radiotherapy: a report from the St Jude Lifetime Cohort study. *J Clin Oncol.* 2015;33(5):492-500.
6. Armstrong GT, Conklin HM, Huang S, et al. Survival and long-term health and cognitive outcomes after low-grade glioma. *Neuro Oncol.* 2011;13(2):223-234.
7. Gleeson HK, Stoeter R, Ogilvy-Stuart AL, Gattamaneni HR, Brennan BM, Shalet SM. Improvements in final height over 25 years in growth hormone (GH)-deficient childhood survivors of brain tumors receiving GH replacement. *J Clin Endocrinol Metab.* 2003;88(8):3682-3689.
8. Children's Oncology Group. Long-term follow-up guidelines for survivors of childhood, adolescent and young adult cancers. Version 4·0–October 2013. 2013. http://www.survivorshipguidelines.org/pdf/LTFUGuidelines_40.pdf (accessed February 4, 2019).
9. Dutch Childhood Oncology Group. Guidelines for follow-up in survivors of childhood cancer 5 years after diagnosis. 2014. https://www.skion.nl/workspace/uploads/vertaling-richtlijn-LATER-versie-final-okt-2014_2.pdf (accessed February 4, 2019).
10. Skinner R, Wallace WHB, Levitt GA, eds. Therapy based on long term follow up practice statement. UK Children's Cancer Study Group Late Effects Group, 2005. http://www.uhb.nhs.uk/Downloads/pdf/CancerPbTherapyBasedLongTermFollowUp.pdf (accessed February 4, 2019).
11. Scottish Intercollegiate Guidelines Network. Long term follow up of survivors of childhood cancer. A national clinical guideline. http://www.sign.ac.uk/pdf/sign132.pdf (accessed February 4, 2019).
12. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol.* 2011;64(4):383-394.
13. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. *Bmj-British Medical Journal.* 2004;328(7454):1490-+.
14. Gibbons RJ, Smith SC, Antman E. American College of Cardiology American Heart Association clinical practice guidelines: Part II - Evolutionary changes in a continuous quality improvement project. *Circulation.* 2003;107(24):3101-3107.
15. Clement SC, Schouten-van Meeteren AY, Boot AM, et al. Prevalence and Risk Factors of Early Endocrine Disorders in Childhood Brain Tumor Survivors: A Nationwide, Multicenter Study. *J Clin Oncol.* 2016;34(36):4362-4370.
16. Gan HW, Phipps K, Aquilina K, Gaze MN, Hayward R, Spoudeas HA. Neuroendocrine Morbidity After Pediatric Optic Gliomas: A Longitudinal Analysis of 166 Children Over 30 Years. *J Clin Endocrinol Metab.* 2015;100(10):3787-3799.
17. Shalitin S, Gal M, Goshen Y, Cohen I, Yaniv I, Phillip M. Endocrine outcome in long-term survivors of childhood brain tumors. *Horm Res Paediatr.* 2011;76(2):113-122.

18. Clayton PE, Shalet SM. Dose dependency of time of onset of radiation-induced growth hormone deficiency. *J Pediatr.* 1991;118(2):226-228.
19. Merchant TE, Rose SR, Bosley C, Wu S, Xiong X, Lustig RH. Growth hormone secretion after conformal radiation therapy in pediatric patients with localized brain tumors. *J Clin Oncol.* 2011;29(36):4776-4780.
20. Schmiegelow M, Lassen S, Poulsen HS, et al. Cranial radiotherapy of childhood brain tumours: growth hormone deficiency and its relation to the biological effective dose of irradiation in a large population based study. *Clin Endocrinol (Oxf).* 2000;53(2):191-197.
21. Schmiegelow M, Feldt-Rasmussen U, Rasmussen AK, Lange M, Poulsen HS, Muller J. Assessment of the hypothalamo-pituitary-adrenal axis in patients treated with radiotherapy and chemotherapy for childhood brain tumor. *J Clin Endocrinol Metab.* 2003;88(7):3149-3154.
22. Gurney JG, Ness KK, Sibley SD, et al. Metabolic syndrome and growth hormone deficiency in adult survivors of childhood acute lymphoblastic leukemia. *Cancer.* 2006;107(6):1303-1312.
23. Shalitin S, Phillip M, Stein J, Goshen Y, Carmi D, Yaniv I. Endocrine dysfunction and parameters of the metabolic syndrome after bone marrow transplantation during childhood and adolescence. *Bone Marrow Transplant.* 2006;37(12):1109-1117.
24. Davis NL, Stewart CE, Moss AD, et al. Growth hormone deficiency after childhood bone marrow transplantation with total body irradiation: interaction with adiposity and age. *Clin Endocrinol (Oxf).* 2015;83(4):508-517.
25. Brennan BM, Rahim A, Mackie EM, Eden OB, Shalet SM. Growth hormone status in adults treated for acute lymphoblastic leukaemia in childhood. *Clin Endocrinol (Oxf).* 1998;48(6):777-783.
26. Leung W, Ahn H, Rose SR, et al. A prospective cohort study of late sequelae of pediatric allogeneic hematopoietic stem cell transplantation. *Medicine (Baltimore).* 2007;86(4):215-224.
27. Eaton BR, Esiashvili N, Kim S, et al. Endocrine outcomes with proton and photon radiotherapy for standard risk medulloblastoma. *Neuro Oncol.* 2016;18(6):881-887.
28. Costin G. Effects of low-dose cranial radiation on growth hormone secretory dynamics and hypothalamic-pituitary function. *Am J Dis Child.* 1988;142(8):847-852.
29. Trivin C, Couto-Silva AC, Sainte-Rose C, et al. Presentation and evolution of organic central precocious puberty according to the type of CNS lesion. *Clin Endocrinol (Oxf).* 2006;65(2):239-245.
30. Brauner R, Malandry F, Rappaport R, et al. Growth and endocrine disorders in optic glioma. *Eur J Pediatr.* 1990;149(12):825-828.
31. Clement SC, Schoot RA, Slater O, et al. Endocrine disorders among long-term survivors of childhood head and neck rhabdomyosarcoma. *Eur J Cancer.* 2016;54:1-10.
32. Kanev PM, Lefebvre JF, Mauseth RS, Berger MS. Growth hormone deficiency following radiation therapy of primary brain tumors in children. *J Neurosurg.* 1991;74(5):743-748.
33. Laughton SJ, Merchant TE, Sklar CA, et al. Endocrine outcomes for children with embryonal brain tumors after risk-adapted craniospinal and conformal primary-site irradiation and high-dose chemotherapy with stem-cell rescue on the SJMB-96 trial. *J Clin Oncol.* 2008;26(7):1112-1118.
34. Sanders JE, Guthrie KA, Hoffmeister PA, Woolfrey AE, Carpenter PA, Appelbaum FR. Final adult height of patients who received hematopoietic cell transplantation in childhood. *Blood.* 2005;105(3):1348-1354.
35. Uday S, Murray RD, Picton S, et al. Endocrine sequelae beyond 10 years in survivors of medulloblastoma. *Clin Endocrinol (Oxf).* 2015;83(5):663-670.
36. Ramanauskiene E, Labanauskas L, Verkauskiene R, Sileikiene R. Early development of endocrine and metabolic consequences after treatment of central nervous system tumors in children. *Medicina (Kaunas).* 2014;50(5):275-280.

37. Merchant TE, Conklin HM, Wu S, Lustig RH, Xiong X. Late effects of conformal radiation therapy for pediatric patients with low-grade glioma: prospective evaluation of cognitive, endocrine, and hearing deficits. *J Clin Oncol.* 2009;27(22):3691-3697.

38. Yock TI, Yeap BY, Ebb DH, et al. Long-term toxic effects of proton radiotherapy for paediatric medulloblastoma: a phase 2 single-arm study. *Lancet Oncol.* 2016;17(3):287-298.

39. Hua C, Wu S, Chemaitilly W, Lukose RC, Merchant TE. Predicting the probability of abnormal stimulated growth hormone response in children after radiotherapy for brain tumors. *Int J Radiat Oncol Biol Phys.* 2012;84(4):990-995.

40. Sklar C, Sarafoglou K, Whittam E. Efficacy of insulin-like growth factor binding protein 3 in predicting the growth hormone response to provocative testing in children treated with cranial irradiation. *Acta Endocrinol (Copenh).* 1993;129(6):511-515.

41. Tillmann V, Shalet SM, Price DA, et al. Serum insulin-like growth factor-I, IGF binding protein-3 and IGFBP-3 protease activity after cranial irradiation. *Horm Res.* 1998;50(2):71-77.

42. Sfeir JG, Kittah NEN, Tamhane SU, et al. Diagnosis of GH Deficiency as a Late Effect of Radiotherapy in Survivors of Childhood Cancers. *J Clin Endocrinol Metab.* 2018;103(8):2785-2793.

43. Rose SR, Lustig RH, Pitukcheewanont P, et al. Diagnosis of hidden central hypothyroidism in survivors of childhood cancer. *J Clin Endocrinol Metab.* 1999;84(12):4472-4479.

44. Darzy KH, Shalet SM. Circadian and stimulated thyrotropin secretion in cranially irradiated adult cancer survivors. *J Clin Endocrinol Metab.* 2005;90(12):6490-6497.

45. Patterson BC, Truxillo L, Wasilewski-Masker K, Mertens AC, Meacham LR. Adrenal function testing in pediatric cancer survivors. *Pediatr Blood Cancer.* 2009;53(7):1302-1307.

46. Sklar CA, Antal Z, Chemaitilly W, et al. Hypothalamic-Pituitary and Growth Disorders in Survivors of Childhood Cancer: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2018;103(8):2761-2784.

47. Growth Hormone Research S. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. GH Research Society. *J Clin Endocrinol Metab.* 2000;85(11):3990-3993.

48. Fleseriu M, Hashim IA, Karavitaki N, et al. Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2016;101(11):3888-3921.

49. Molitch ME, Clemmons DR, Malozowski S, et al. Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2006;91(5):1621-1634.

50. Junnila RK, Strasburger CJ, Bidlingmaier M. Pitfalls of insulin-like growth factor-i and growth hormone assays. *Endocrinol Metab Clin North Am.* 2015;44(1):27-34.

51. Persani L, Brabant G, Dattani M, et al. 2018 European Thyroid Association (ETA) Guidelines on the Diagnosis and Management of Central Hypothyroidism. *Eur Thyroid J.* 2018;7(5):225-237.

52. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2018;103(5):1715-1744.

53. Bakker B, Oostdijk W, Geskus RB, Stokvis-Brantsma WH, Vossen JM, Wit JM. Growth hormone (GH) secretion and response to GH therapy after total body irradiation and haematopoietic stem cell transplantation during childhood. *Clin Endocrinol (Oxf).* 2007;67(4):589-597.

54. Brignardello E, Felicetti F, Castiglione A, et al. GH replacement therapy and second neoplasms in adult survivors of childhood cancer: a retrospective study from a single institution. *J Endocrinol Invest.* 2015;38(2):171-176.

55. Ergun-Longmire B, Mertens AC, Mitby P, et al. Growth hormone treatment and risk of second neoplasms in the childhood cancer survivor. *J Clin Endocrinol Metab.* 2006;91(9):3494-3498.

56. Leung W, Rose SR, Zhou Y, et al. Outcomes of growth hormone replacement therapy in survivors of childhood acute lymphoblastic leukemia. *J Clin Oncol.* 2002;20(13):2959-2964.
57. Mackenzie S, Craven T, Gattamaneni HR, Swindell R, Shalet SM, Brabant G. Long-term safety of growth hormone replacement after CNS irradiation. *J Clin Endocrinol Metab.* 2011;96(9):2756-2761.
58. Patterson BC, Chen Y, Sklar CA, et al. Growth hormone exposure as a risk factor for the development of subsequent neoplasms of the central nervous system: a report from the childhood cancer survivor study. *J Clin Endocrinol Metab.* 2014;99(6):2030-2037.
59. Sklar CA, Mertens AC, Mitby P, et al. Risk of disease recurrence and second neoplasms in survivors of childhood cancer treated with growth hormone: a report from the Childhood Cancer Survivor Study. *J Clin Endocrinol Metab.* 2002;87(7):3136-3141.
60. Woodmansee WW, Zimmermann AG, Child CJ, et al. Incidence of second neoplasm in childhood cancer survivors treated with GH: an analysis of GeNeSIS and HypoCCS. *Eur J Endocrinol.* 2013;168(4):565-573.
61. Tamhane S, Sfeir JG, Kittah NEN, et al. GH Therapy in Childhood Cancer Survivors: A Systematic Review and Meta-Analysis. *J Clin Endocrinol Metab.* 2018;103(8):2794-2801.
62. Corrias A, Picco P, Einaudi S, et al. Growth hormone treatment in irradiated children with brain tumors. *J Pediatr Endocrinol Metab.* 1997;10(1):41-49.
63. Ogilvy-Stuart AL, Ryder WD, Gattamaneni HR, Clayton PE, Shalet SM. Growth hormone and tumour recurrence. *BMJ.* 1992;304(6842):1601-1605.
64. Packer RJ, Boyett JM, Janss AJ, et al. Growth hormone replacement therapy in children with medulloblastoma: use and effect on tumor control. *J Clin Oncol.* 2001;19(2):480-487.
65. Swerdlow AJ, Reddingius RE, Higgins CD, et al. Growth hormone treatment of children with brain tumors and risk of tumor recurrence. *J Clin Endocrinol Metab.* 2000;85(12):4444-4449.
66. Allen DB, Backeljauw P, Bidlingmaier M, et al. GH safety workshop position paper: a critical appraisal of recombinant human GH therapy in children and adults. *Eur J Endocrinol.* 2016;174(2):P1-9.
67. Grimberg A, DiVall SA, Polychronakos C, et al. Guidelines for Growth Hormone and Insulin-Like Growth Factor-I Treatment in Children and Adolescents: Growth Hormone Deficiency, Idiopathic Short Stature, and Primary Insulin-Like Growth Factor-I Deficiency. *Horm Res Paediatr.* 2016;86(6):361-397.
68. Molitch ME, Clemmons DR, Malozowski S, Merriam GR, Vance ML, Endocrine S. Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2011;96(6):1587-1609.
69. Ho KK, Participants GHDCW. Consensus guidelines for the diagnosis and treatment of adults with GH deficiency II: a statement of the GH Research Society in association with the European Society for Pediatric Endocrinology, Lawson Wilkins Society, European Society of Endocrinology, Japan Endocrine Society, and Endocrine Society of Australia. *Eur J Endocrinol.* 2007;157(6):695-700.
70. Matthews D, Bath L, Hogler W, Mason A, Smyth A, Skae M. Hormone supplementation for pubertal induction in girls. *Arch Dis Child.* 2017;102(10):975-980.
71. Carel JC, Eugster EA, Rogol A, et al. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. *Pediatrics.* 2009;123(4):e752-762.

Supplementary material

Clinical questions

WG1; Who needs surveillance?

Clinical questions concerning CAYA cancer survivors with a history of CNS tumor

1. What is the risk of HP dysfunction in CAYA cancer survivors (CNS tumor) after radiotherapy?

   a. What is the risk of HP dysfunction in CAYA cancer survivors (CNS tumor) treated with cranial radiotherapy versus no cranial radiotherapy?
   b. What is the risk of HP dysfunction in CAYA cancer survivors (CNS tumor) treated with higher versus lower doses radiotherapy?
   c. What is the risk of HP dysfunction in CAYA cancer survivors (CNS tumor) treated with different fractionation schedules?
   d. What is the risk of HP dysfunction in CAYA cancer survivors (CNS tumor) treated with different types of radiotherapy (e.g. electron, IMRT, brachytherapy, proton beam therapy)?
   e. What is the risk of HP dysfunction in CAYA cancer survivors (CNS tumor) treated with radiotherapy at different fields (other than cranial RT)?

2. What is the risk of HP dysfunction in CAYA cancer survivors (CNS tumor) after chemotherapy?

   a. What is the risk of HP dysfunction in CAYA cancer survivors (CNS tumor) treated with both chemotherapy and radiotherapy?
   b. What is the risk of HP dysfunction in CAYA cancer survivors (CNS tumor) treated chemotherapy, but no radiotherapy?

3. What is the risk of HP dysfunction in CAYA cancer survivors (CNS tumor) after neurosurgery?

   a. What is the risk of HP dysfunction in CAYA cancer survivors (CNS tumor) treated with neurosurgery?
   b.What is the risk of HP dysfunction in CAYA cancer survivors (CNS tumor) treated with higher versus lower numbers of neurosurgeries?

4. Are there other etiological risk factors associated with the risk of HP dysfunction in CAYA cancer survivors (CNS tumor)?

   a. What is the risk of gender?
   b. What is the risk of ethnicity/race
   c. What is the risk of neurofibromatosis
   d. What is the risk of hydrocephalus/shunt
   e. What is the risk of tumor histology/type
   f. What is the risk of genetic profile of the patient
   g. What is the risk of age at diagnosis/treatment
   h. What is the risk of age at follow-up
   i. What is the risk of time since diagnosis/treatment
   j. What is the risk of treatment era

Clinical questions concerning CAYA cancer survivors with a history of non-CNS tumor

5. What is the risk of HP dysfunction in CAYA cancer survivors (non-CNS tumor) after radiotherapy?

a. What is the risk of HP dysfunction in CAYA cancer survivors (non-CNS tumor) treated with radiotherapy exposing (parts) of the head and neck region versus no radiotherapy?
b. What is the risk of HP dysfunction in CAYA cancer survivors (non-CNS tumor) treated with higher versus lower doses radiotherapy?
c. What is the risk of HP dysfunction in CAYA cancer survivors (non-CNS tumor) treated with TBI versus no TBI?
d. What is the risk of HP dysfunction in CAYA cancer survivors (non-CNS tumor) treated with different fractionation schedules?
e. What is the risk of HP dysfunction in CAYA cancer survivors (non-CNS tumor) treated with different types of radiotherapy (e.g. electron, IMRT, brachytherapy, proton beam therapy)?

6. What is the risk of HP dysfunction in CAYA cancer survivors (non-CNS tumor) treated with both chemotherapy and radiotherapy?

7. What is the risk of HP dysfunction in CAYA cancer survivors (non-CNS tumor) treated with chemotherapy, but no radiotherapy?

8. What is the risk of HP dysfunction in brain injured (i.e. increased intracranial pressure, meningitis, cerebral thrombosis, cerebral bleeding, cerebral leukemia, abscesses, drug/chemo induced encephalopathy or other cerebral inflammation such as encephalitis, fungal infections, vasculitis or graft versus host diseases) CAYA cancer survivors (non-CNS tumor)?

9. Are there other etiological risk factors associated with the risk of HP dysfunction in CAYA cancer survivors (non-CNS tumor)?

a. What is the risk of gender?
b. What is the risk of ethnicity/race
c. What is the risk of tumor histology/type
d. What is the risk of genetic profile of the patient
e. What is the risk of age at diagnosis/treatment
f. What is the risk of age at follow-up
g. What is the risk of time since diagnosis/treatment

WG2; When should surveillance be initiated? At what frequency and for how long should surveillance be performed?

1. When should surveillance for HP dysfunction in CAYA cancer survivors (CNS tumor and non-CNS tumor) be initiated?

a. What is the latency time to develop HP dysfunction in CAYA cancer survivors (CNS tumor and non-CNS tumor) treated with potentially high-risk treatment?
b. Are there any modifying factors (e.g. steroids, surgery) that alter the latency time to develop HP dysfunction in CAYA cancer survivors (CNS tumor and non-CNS tumor) treated with potentially high-risk treatment?
c. What is the latency time to develop HP dysfunction in CAYA cancer survivors (non-CNS tumor) who had brain injuries other than the malignancy (e.g. hydrocephalus or infection) and are there any modifiers?
d. What is the order of occurrence in which HP dysfunction occurs in CAYA cancer survivors (CNS tumor and non-CNS tumor) who have been treated with potentially high-risk treatment?
e. What is the order of occurrence in which HP dysfunction occurs in CAYA cancer survivors (CNS tumor) with a tumor in the sellar and suprasellar region versus CNS tumors located elsewhere in the brain?

f. What is the order of occurrence in which HP dysfunction occurs in CAYA cancer survivors (non-CNS tumor) who have had brain injury?

2. For how long should surveillance for HP dysfunction continue in CAYA cancer survivors (CNS tumor and non-CNS tumor) who had (repeatedly) a negative screen?

a. Does the risk of developing HP dysfunction change (increase or decrease) over time in CAYA cancer survivors (CNS tumor and non-CNS tumor)?
   i. What is the timing of such change?
   ii. Is there a plateau in the cumulative incidence of HP dysfunction in CAYA cancer survivors (CNS tumor and non-CNS tumor), and if so when?
b. Are there any modifying factors that alter the cumulative incidence to develop HP dysfunction in CAYA cancer survivors (CNS tumor and non-CNS tumor) treated with potentially high-risk treatment?

WG3; What surveillance modality should be used?

1. Which screening modality is most sensitivity and specific for detecting GHD in CAYA cancer survivors?

a. What is the diagnostic value of IGF-1 and IGFBP-3 measurements versus GH stimulation tests (preferably gold standard, ITT or glucagon) for detecting GHD in *pre- and peri-pubertal* cancer survivors?
b. What is the diagnostic value of height plotted in a growth chart versus GH stimulation tests (preferably gold standard, ITT or glucagon) for detecting GHD in *pre- and peri-pubertal* cancer survivors?
c. What is the diagnostic value of IGF-1 and IGFBP-3 measurements versus GH stimulation tests (preferably gold standard, ITT or glucagon) for detecting GHD in *adult* cancer survivors?

2.Which screening modality is most sensitive and specific for detecting TSHD in CAYA cancer survivors?

a. What is the diagnostic value of FT4, FT3, TSH and FT4/FT3 ratio and serial measurements for detecting TSHD versus a TRH test or nocturnal TSH surge in CAYA cancer survivors (or the normal population)?
b. What are the confounders which bias the testing results of the thyrotrophic axis?

3. Which screening modality is most sensitive and specific for detecting LH/FSHD or CPP in CAYA cancer survivors?

a. What is the diagnostic value of Tanner stage, bone age, LH, FSH and sex steroids measurements for detecting central hypogonadism in pre-pubertal girls at B1 >12 years or boys age 13 with pre-pubertal testes?
b. What is the inter-observer variability and likelihood performance for defining Tanner stages between health care providers from different specialties?

4. Which screening modality is most sensitivity and specific for detecting ACTHD in CAYA cancer survivors?

a. What is the diagnostic value of morning plasma cortisol (total and free), ACTH, saliva cortisol or morning glucose (in young children) measurements versus dynamic testing (preferably ITT) for detecting ACTHD in pediatric cancer survivors?

b. What is the diagnostic value of morning plasma cortisol (total and free), ACTH and saliva cortisol measurements versus dynamic testing (preferably ITT) for detecting ACTHD in adult cancer survivors?
c. What is the influence of steroid use (topical/oral/inhaled) on the testing results of the corticotropic axis for detecting ACTHD in pediatric cancer survivors?
d. What are the confounders in CAYA cancer survivors which bias the testing results of the corticotropic axis?

5. Which screening modality is most sensitive and specific for detecting CPP in childhood cancer survivors?

- a. What is the diagnostic value of screening with Tanner stage and/or growth velocity versus measuring LH, FSH and sex steroid levels or LHRH (or GnRH agonist) testing, or pelvic ultrasound (only in girls) or bone age in girls B2 <8 years or boys with pubertal testis (>4mL) or other signs of virilization <9y/o for detecting CPP?
- b. What is the diagnostic value of testes volume for detecting CPP changed in boys treated with gonadotoxic therapy?

6. What are the pitfalls in the interpretation of different screening modalities for HP dysfunction?

7. What are the pitfalls of other endocrine organs being damaged interfering with the test results for pituitary damage (direct gonadal damage, direct thyroidal damage et cetera)?

8. Are there screening modalities that are not appropriate and should be explicitly discouraged?

WG4; What should be done when abnormalities are identified?

1. What are the potential benefits of treatment for HP dysfunction in CAYA cancer survivors?
   a. What are potential benefits of treatment for GHD in pediatric/adult cancer survivors?
   b. What are potential benefits of treatment for TSHD in pediatric/adult cancer survivors?
   c. What are potential benefits of treatment for LH/FSHD in pediatric/adult cancer survivors?
   d. What are potential benefits of treatment for ACTHD in pediatric/adult cancer survivors?
   e. What are potential benefits of treatment for CPP in pediatric/adult cancer survivors?

2. What are the potential harms of treatment for HP dysfunction in CAYA cancer survivors?
   a. What are potential harms of treatment for GHD in pediatric/adult cancer survivors?
   b. What are potential harms of treatment for TSHD in pediatric/adult cancer survivors?
   c. What are potential harms of treatment for LH/FSHD in pediatric/adult cancer survivors?
   d. What are potential harms of treatment for ACTHD in pediatric/adult cancer survivors?
   e. What are potential harms of treatment for CPP in pediatric/adult cancer survivors?

Search strategies

Search strategies: WG1 "Who needs surveillance"

Question 1

Search 1: Childhood brain tumors	PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR brain tumor* OR brain tumour* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system tumor* OR central nervous system tumour* OR brain cancer* OR brain neoplasm* OR intracranial neoplasm* OR astrocytoma OR astrocytom* OR chondrosarcoma OR chondrosarcoma* OR ependymoma OR ependymom* OR germ cell tumor OR germ cell tumor* OR glioblastoma OR glioblastoma* OR glioma OR gliom* OR hemangioma OR hemangioma* OR lipoma OR lipom* OR meningioma OR meningioma* OR schwannoma OR pineal tumor OR pineal tumor* OR chordoma OR chordom* OR oligodendroglioma OR oligodendrogliom* OR rhabdoid tumor OR rhabdoid tumor* OR craniopharyngioma OR craniopharyngiom* OR pituitary tumor OR pituitary tumor* OR CNS embryonal tumor OR CNS embryonal tumor* OR pineoblastoma OR pineoblastom* OR medulloepithelioma OR medulloepitheliom* OR ependymoblastoma OR ependymoblastom*
Search 2: Radiotherapy extended Radiotherapy dosimetry Radiotherapy fields cranial, TBI	((Radiotherapy OR radiation OR radiation therapy OR irradiation OR irradiat* OR radiation injuries OR injuries, radiation OR injury, radiation OR radiation injury OR radiation syndrome OR radiation syndromes OR syndrome radiation OR radiation sickness OR radiation sicknesses OR sickness radiation OR radiation* OR irradiation OR radiations OR stereotactic RT OR stereotactic radiotherapy[tiab] OR gamma knife OR intensity modulated radiotherapy OR IMRT OR radiotherapy, intensity-modulated[mh] OR three dimensional OR 3D OR 3d CRT OR image guided radiotherapy OR IGRT OR radiotherapy, image-guided[mh] OR photon radiotherapy OR XRT OR "photons/therapeutic use"[Mesh] OR proton radiotherapy OR PRT OR proton therapy OR proton radiation OR proton beam OR carbon ion radiotherapy) OR (radiometry OR radiation dosage OR radiation dose OR radiation doses OR radiation dosis OR radiation dosage* OR radiation dosimetry OR radiation dosimetr* OR dose-response relationship, radiation OR radiometr* OR radiotherapy dosage OR radiotherapy[sh] OR radiotherapy/adverse effects OR irradiation dose OR radiotherapy dose OR dose calculation OR near beam dose OR in beam dose OR outside beam dose OR out of beam dose OR radiation/epidemiology OR Radiation monitoring OR Organs at risk OR radiation effects[sh] OR radiation injury OR radiation injuries OR radiation OR Radiotherapy/complications[Mesh])) AND (cranial OR craniospinal OR head[tiab] OR skull OR TBI OR Total body OR whole body OR total body* OR body whole* OR cranial irradiation [mh] OR craniospinal irradiation [mh])

Search 3: HP disorders general	hypothalamic diseases OR pituitary diseases OR hypopituitarism OR pituitary hormones, anterior[mh] OR anterior pituitary hormone deficiency OR endocrine system diseases[mh] OR endocrine disorder OR hypophyseal deficiency OR (pituitary AND (dysfunction* OR hypofunction)) OR panhypopituitarism OR combined pituitary hormone deficiency OR multiple pituitary hormone deficiency OR (("endocrine system"[MeSH Terms] OR (endocrine AND system) OR endocrine system OR endocrine) AND ("complications"[Subheading] OR complications OR sequelae))	
Search 4: Growth hormone deficiency	(growth hormone OR GHD OR GH) AND (deficien* OR disorder OR impairment OR deviation)	
Search 5: Central hypothyroidism	((Thyroid stimulation hormone OR TSH OR Thyrotropin releasing hormone OR TRH OR thyroxine OR tri iodothyronine OR triiodothyronine) AND (deficiency OR disease)) OR (thyroid hormones[mh] AND (deficiency OR disease)) OR thyroid diseas* OR hypothyroidism[mh] OR hypothyroidism* OR thyroxine OR levo-thyroxine OR tri-iodothyronine	
Search 6: Central hypocortisolism	((adrenocorticotropic hormone[mh] OR adrenocorticotropic hormone* OR ACTH OR hydrocortisone) AND (insufficiency OR deficiency)) OR ((adrenal OR hydrocortisone) AND (insufficiency OR deficiency OR crisis)) OR hypocortisolism OR hypocortisolism* OR Addison disease[mh]	
Search 7: Hypogonadotropic hypogonadism	hypogonadotropic hypogonadism OR hypogonadism[mh] OR (infertility AND pituitary) OR ((follicle stimulating hormone OR FSH OR gonadotropin* OR luteinizing hormone OR LH OR estrogen OR testosterone) AND deficiency) OR ((puberty OR menarche OR sexual development) AND delay*) OR ((gonadotropin OR estrogen OR testosterone) AND (deficiency OR insufficiency))	
Search 8: Central Precocious puberty	(precocious AND (sexual OR puberty pubarche OR menarche)) OR CPP OR puberty, precocious[mh] OR premature puberty OR breast development puberty OR skeletal maturation OR epiphyseal plate closure OR bone age* OR skeletal age*) OR thelarche	
Search 1 AND 2 AND (3 OR 4 OR 5 OR 6 OR 7 OR 8) Filters: published from 1990 onwards; Humans; English; NOT (case reports or case reports)		**873 (original) 37 (updated)**

Question 2

Search 1: Childhood brain tumors	PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR brain tumor* OR brain tumour* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system tumor* OR central nervous system tumour* OR brain cancer* OR brain neoplasm* OR intracranial neoplasm* OR astrocytoma OR astrocytom* OR chondrosarcoma OR chondrosarcoma* OR ependymoma OR ependymom* OR germ cell tumor OR germ cell tumor* OR glioblastoma OR glioblastoma* OR glioma OR gliom* OR hemangioma OR hemangioma* OR lipoma OR lipom* OR meningioma OR meningioma* OR schwannoma OR pineal tumor OR pineal tumor* OR chordoma OR chordom* OR oligodendroglioma OR oligodendrogliom* OR rhabdoid tumor OR rhabdoid tumor* OR craniopharyngioma OR craniopharyngiom* OR pituitary tumor OR pituitary tumor* OR CNS embryonal tumor OR CNS embryonal tumor* OR pineoblastoma OR pineoblastom* OR medulloepithelioma OR medulloepitheliom* OR ependymoblastoma OR ependymoblastom*

Search 2: Chemotherapy	Antineoplastic Protocols OR Antineoplastic Combined Chemotherapy Protocols OR Chemoradiotherapy OR Chemoradiotherapy, Adjuvant OR Chemotherapy, Adjuvant OR Consolidation Chemotherapy OR Induction chemotherapy OR Maintenance chemotherapy OR Chemotherapy, Cancer, Regional Perfusion OR Antineoplastic agents OR chemotherap*	
Search 3: HP dysfunction	hypothalamic diseases OR pituitary diseases OR hypopituitarism OR pituitary hormones, anterior[mh] OR anterior pituitary hormone deficiency OR endocrine system diseases[mh] OR endocrine disorder OR hypophyseal deficiency OR (pituitary AND (dysfunction* OR hypofunction)) OR panhypopituitarism OR combined pituitary hormone deficiency OR multiple pituitary hormone deficiency OR (("endocrine system"[MeSH Terms] OR (endocrine AND system) OR endocrine system OR endocrine) AND ("complications"[Subheading] OR complications OR sequelae))	
Search 4: Survivors OR late effects	Survivor OR survivors OR survivor* OR long term survivor OR long term survivors OR long term survivor* OR survivo* OR surviving OR long term survival[tiab] OR survival[mh] OR "late effect" OR "late effects" OR "late effect*" OR "late side effect" OR "late side effects" OR "late side effect*" OR "late adverse effect" OR "late adverse effects" OR "late adverse effect*" OR long term effect[tiab] OR long term effect* OR long term adverse effects[mh] OR follow up studie* OR follow up study OR aftercare [mh] OR aftercare* OR after treatment [tiab]	
Search 1 AND 2 AND 3 AND 4 Filters: published from 1990 onwards; Humans; English; NOT (case reports or case reports)		**1734 (original) 180 (updated)**

Question 3

Search 1: Childhood brain tumors	PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR brain tumor* OR brain tumour* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system tumor* OR central nervous system tumour* OR brain cancer* OR brain neoplasm* OR intracranial neoplasm* OR OR astrocytoma OR astrocytom* OR chondrosarcoma OR chondrosarcoma* OR ependymoma OR ependymom* OR germ cell tumor OR germ cell tumor* OR glioblastoma OR glioblastoma* OR glioma OR gliom* OR hemangioma OR hemangioma* OR lipoma OR lipom* OR meningioma OR meningioma* OR schwannoma OR pineal tumor OR pineal tumor* OR chordoma OR chordom* OR oligodendroglioma OR oligodendrogliom* OR rhabdoid tumor OR rhabdoid tumor* OR craniopharyngioma OR craniopharyngiom* OR pituitary tumor OR pituitary tumor* OR CNS embryonal tumor OR CNS embryonal tumor* OR pineoblastoma OR pineoblastom* OR medulloepithelioma OR medulloepitheliom* OR ependymoblastoma OR ependymoblastom*
Search 2: Neurosurgery	Neurosurgery OR neurosurger* OR neurosurgical procedure OR neurosurgical procedure* OR (brain[tiab] AND surgery) OR (cranial* AND surger*)
Search 3: HP dysfunction	hypothalamic diseases OR pituitary diseases OR hypopituitarism OR pituitary hormones, anterior[mh] OR anterior pituitary hormone deficiency OR endocrine system diseases[mh] OR endocrine disorder OR hypophyseal deficiency OR (pituitary AND (dysfunction* OR hypofunction)) OR panhypopituitarism OR combined pituitary hormone deficiency OR multiple pituitary hormone deficiency OR (("endocrine system"[MeSH Terms] OR (endocrine AND system) OR endocrine system OR endocrine) AND ("complications"[Subheading] OR complications OR sequelae))

Search 4: Survivors OR late effects	Survivor OR survivors OR survivor* OR long term survivor OR long term survivors OR long term survivor* OR survivo* OR surviving OR long term survival[tiab] OR survival[mh] OR "late effect" OR "late effects" OR "late effect*" OR "late side effect" OR "late side effects" OR "late side effect*" OR "late adverse effect" OR "late adverse effects" OR "late adverse effect*" OR long term effect[tiab] OR long term effect* OR long term adverse effects[mh] OR follow up studie* OR follow up study OR aftercare [mh] OR aftercare* OR after treatment [tiab]	
Search 1 AND 2 AND 3 AND 4 Filters: published from 1990 onwards; Humans; English; NOT (case reports or case reports)		**1134 (original) 82 (updated)**

Question 4; Studies answering question 4 will be identified through the other searches of WG1 "who needs surveillance".

Question 5

Search 1: Childhood cancer no brain tumors	leukemia OR leukemi* OR leukaemi* OR (childhood ALL) OR AML OR OR acute lymphocytic leukemia OR acute myeloid leukemia lymphoma OR lymphom* OR hodgkin OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR sarcoma, Ewing's OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR retinoblastoma OR retinoblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR pediatric oncology OR paediatric oncology OR childhood cancer OR childhood tumor OR childhood tumors	
Search 2: Radiotherapy extended Radiotherapy fields cranial, head and neck, TBI	(Radiotherapy OR radiation OR radiation therapy OR irradiation OR irradiat* OR radiation injuries OR injuries, radiation OR injury, radiation OR radiation injury OR radiation syndrome OR radiation syndromes OR syndrome radiation OR radiation sickness OR radiation sicknesses OR sickness radiation OR radiation* OR irradiation OR radiations OR stereotactic RT OR stereotactic radiotherapy[tiab] OR gamma knife OR intensity modulated radiotherapy OR IMRT OR radiotherapy, intensity-modulated[mh] OR three dimensional OR 3D OR 3d CRT OR image guided radiotherapy OR IGRT OR radiotherapy, image-guided[mh] OR photon radiotherapy OR XRT OR "photons/therapeutic use"[Mesh] OR proton radiotherapy OR PRT OR proton therapy OR proton radiation OR proton beam OR carbon ion radiotherapy) AND (Cranial OR craniospinal OR head[tiab] OR neck[tiab] OR skull OR mantle field[tiab] OR medulla oblongata OR Waldeyer* ring OR mediastinum OR supraclavicular OR nasopharynx OR orbital OR TBI OR Total body OR whole body OR total body* OR body whole* OR cranial irradiation[mh] OR craniospinal irradiation [mh])	
Search 3: HP dysfunction	hypothalamic diseases OR pituitary diseases OR hypopituitarism OR pituitary hormones, anterior[mh] OR anterior pituitary hormone deficiency OR endocrine system diseases[mh] OR endocrine disorder OR hypophyseal deficiency OR (pituitary AND (dysfunction* OR hypofunction)) OR panhypopituitarism OR combined pituitary hormone deficiency OR multiple pituitary hormone deficiency OR (("endocrine system"[MeSH Terms] OR (endocrine AND system) OR endocrine system OR endocrine) AND ("complications"[Subheading] OR complications OR sequelae))	
Search 1 AND 2 AND 3 Filters: published from 1990 onwards; Humans; English; NOT (case reports or case reports)		**448 (original) 34 (updated)**

Question 6,7

Search 1: Childhood cancer no brain tumors	leukemia OR leukemi* OR leukaemi* OR (childhood ALL) OR AML OR OR acute lymphocytic leukemia OR acute myeloid leukemia lymphoma OR lymphom* OR hodgkin OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR sarcoma, Ewing's OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR retinoblastoma OR retinoblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR pediatric oncology OR paediatric oncology OR childhood cancer OR childhood tumor OR childhood tumors	
Search 2: Chemotherapy	Antineoplastic Protocols OR Antineoplastic Combined Chemotherapy Protocols OR Chemoradiotherapy OR Chemoradiotherapy, Adjuvant OR Chemotherapy, Adjuvant OR Consolidation Chemotherapy OR Induction chemotherapy OR Maintenance chemotherapy OR Chemotherapy, Cancer, Regional Perfusion OR Antineoplastic agents OR chemotherap*	
Search 3: HP dysfunction	hypothalamic diseases OR pituitary diseases OR hypopituitarism OR pituitary hormones, anterior[mh] OR anterior pituitary hormone deficiency OR endocrine system diseases[mh] OR endocrine disorder OR hypophyseal deficiency OR (pituitary AND (dysfunction* OR hypofunction)) OR panhypopituitarism OR combined pituitary hormone deficiency OR multiple pituitary hormone deficiency OR (("endocrine system"[MeSH Terms] OR (endocrine AND system) OR endocrine system OR endocrine) AND ("complications"[Subheading] OR complications OR sequelae))	
Search 4: Survivors OR late effects	Survivor OR survivors OR survivor* OR long term survivor OR long term survivors OR long term survivor* OR survivo* OR surviving OR long term survival[tiab] OR survival[mh] OR "late effect" OR "late effects" OR "late effect*" OR "late side effect" OR "late side effects" OR "late side effect*" OR "late adverse effect" OR "late adverse effects" OR "late adverse effect*" OR long term effect[tiab] OR long term effect* OR long term adverse effects[mh] OR follow up studie* OR follow up study OR aftercare [mh] OR aftercare* OR after treatment [tiab]	
Search 1 AND 2 AND 3 AND 4 Filters: published from 1990 onwards; Humans; English; NOT (case reports or case reports)		**1326 (original) 123 (updated)**

Question 8

Search 1: Childhood cancer no brain tumors	leukemia OR leukemi* OR leukaemi* OR (childhood ALL) OR AML OR OR acute lymphocytic leukemia OR acute myeloid leukemia lymphoma OR lymphom* OR hodgkin OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR sarcoma, Ewing's OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR retinoblastoma OR retinoblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR pediatric oncology OR paediatric oncology OR childhood cancer OR childhood tumor OR childhood tumors
Search 2: Brain injury	intracranial pressure[mh] OR intracranial pressur* OR meningitis OR intracranial thrombosis[mh] OR cerebral thrombosis OR cerebral bleeding OR cerebral hemorrhage OR (cerebral[tiab] AND leukemi*[tiab]) OR brain abscess OR brain abscess* OR encephalopathy OR cerebral inflammation OR brain inflammation OR encephalitis OR (brain AND fungal infection*) OR (vasculitis AND (brain OR central nervous system)) OR (graft versus host disease AND brain) OR hydrocephalus

Search 3: HP dysfunction	hypothalamic diseases OR pituitary diseases OR hypopituitarism OR pituitary hormones, anterior[mh] OR anterior pituitary hormone deficiency OR endocrine system diseases[mh] OR endocrine disorder OR hypophyseal deficiency OR (pituitary AND (dysfunction* OR hypofunction)) OR panhypopituitarism OR combined pituitary hormone deficiency OR multiple pituitary hormone deficiency OR ((“endocrine system”[MeSH Terms] OR (endocrine AND system) OR endocrine system OR endocrine) AND (“complications”[Subheading] OR complications OR sequelae))	
Search 4: Survivors OR late effects	Survivor OR survivors OR survivor* OR long term survivor OR long term survivors OR long term survivor* OR survivo* OR surviving OR long term survival[tiab] OR survival[mh] OR “late effect” OR “late effects” OR “late effect*” OR “late side effect” OR “late side effects” OR “late side effect*” OR “late adverse effect” OR “late adverse effects” OR “late adverse effect*” OR long term effect[tiab] OR long term effect* OR long term adverse effects[mh] OR follow up studie* OR follow up study OR aftercare [mh] OR aftercare* OR after treatment [tiab]	
Search 1 AND 2 AND 3 AND 4 Filters: published from 1990 onwards; Humans; English; NOT (case reports or case reports)		**619 (original) 90 (updated)**

Question 9; Studies answering question 9 will be identified through the other searches of WG1 “who needs surveillance”.

Search strategies: WG2 “When should surveillance be initiated? At what frequency and for how long should surveillance be performed?”

Studies answering questions 1 and 2 will be identified through the searches of WG1 “who needs surveillance”.

Search strategies: WG3 “What surveillance modality should be used?”

Question 1

Search 1: Childhood cancer	((leukemia OR leukemi* OR leukaemi* OR (childhood ALL) OR AML OR lymphoma OR lymphom* OR hodgkin OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR sarcoma, Ewing’s OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom*) OR (pediatric oncology OR paediatric oncology) OR (childhood cancer OR childhood tumor OR childhood tumors)) OR (brain tumor* OR brain tumour* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system tumor* OR central nervous system tumour* OR brain cancer* OR brain neoplasm* OR intracranial neoplasm*) OR (leukemia, lymphocytic, acute[mh])

Search 2: Growth hormone deficiency - specific	(growth hormone OR GHD OR GH) AND (deficien* OR disorder OR impairment OR deviation)	
Search 3: Diagnostic test	insulin-like growth factor I OR insulin-like growth factor 1 OR IGF-1 OR IGF-I OR insulin like growth factor I OR insulin like growth factor 1 OR somatomedin C OR insulin-like somatomedin peptide I OR insulin like somatomedin peptide I OR insulin-like somatomedin peptide 1 OR insulin like somatomedin peptide 1 OR insulin-like growth factor binding protein 3 OR insulin like growth factor binding protein 3 OR IGF-binding protein 3 OR IGF binding protein 3 OR IGFBP-3 OR ((growth hormone stimulation OR GH stimulation) AND (test[tiab] OR testing)) OR glucagon stimulation test[tiab] OR arginine test[tiab] OR clonidine test [tiab] OR ((GHRH OR growth hormone releasing hormone) AND (test[tiab] OR assay)) OR insulin tolerance test[tiab] OR ITT OR (propranolol AND (l dopa OR levodopa)) OR human growth hormone/blood[mh] OR growth hormone overnight	
Search 1 AND 2 AND 3 Filters: published from 1990 onwards; Humans; English; NOT (case reports or case reports)		**904 (original) 70 (updated)**

Question 2

Search 1: Childhood cancer	((leukemia OR leukemi* OR leukaemi* OR (childhood ALL) OR AML OR lymphoma OR lymphom* OR hodgkin OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR sarcoma, Ewing's OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom*) OR (pediatric oncology OR paediatric oncology) OR (childhood cancer OR childhood tumor OR childhood tumors)) OR (brain tumor* OR brain tumour* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system tumor* OR central nervous system tumour* OR brain cancer* OR brain neoplasm* OR intracranial neoplasm*) OR (leukemia, lymphocytic, acute[mh])	
Search 2: Central hypothyroidism	((Thyroid stimulation hormone OR TSH OR Thyrotropin releasing hormone OR TRH OR thyroxine OR tri iodothyronine OR triiodothyronine) AND (deficiency OR disease)) OR (thyroid hormones[mh] AND (deficiency OR disease)) OR thyroid diseas* OR hypothyroidism[mh] OR hypothyroidism* OR thyroxine OR levo-thyroxine OR tri-iodothyronine	
Search 3: Diagnostic test	FT4 OR TSH OR FT3 OR FT3 FT4 ratio* OR (TRH AND (test[tiab] OR surge OR value* OR peak OR nadir OR measurement OR assay OR concentration*)) OR Thyroxine/blood[mh] OR thyrotropin/blood[mh] OR thyroid hormones/blood[mh]	
Search 1 AND 2 AND 3 Filters: published from 1990 onwards; Humans; English; NOT (case reports or case reports)		**778 (original) 75 (updated)**

Question 3, 5

Search 1: Childhood cancer	((leukemia OR leukemi* OR leukaemi* OR (childhood ALL) OR AML OR lymphoma OR lymphom* OR hodgkin OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR sarcoma, Ewing's OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom*) OR (pediatric oncology OR paediatric oncology) OR (childhood cancer OR childhood tumor OR childhood tumors)) OR (brain tumor* OR brain tumour* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system tumor* OR central nervous system tumour* OR brain cancer* OR brain neoplasm* OR intracranial neoplasm*) OR (leukemia, lymphocytic, acute[mh])	
Search 2: Hypogonadotropic hypogonadism	hypogonadotropic hypogonadism OR hypogonadism[mh] OR (infertility AND pituitary) OR ((follicle stimulating hormone OR FSH OR gonadotropin* OR luteinizing hormone OR LH OR estrogen OR testosterone) AND deficiency) OR ((puberty OR menarche OR sexual development) AND delay*) OR ((gonadotropin OR estrogen OR testosterone) AND (deficiency OR insufficiency))	
Search 3: Central precocious puberty	(precocious AND (sexual OR puberty OR pubarche OR menarche)) OR CPP OR puberty, precocious[mh] OR premature puberty OR breast development puberty OR skeletal maturation OR epiphyseal plate closure OR bone age* OR skeletal age*) OR thelarche	
Search 4: Diagnostic test	(tanner[tiab] AND (scale* OR stage* OR staging)) OR bone age* OR skeletal age* OR ((follicle stimulating hormone OR FSH OR gonadotropin* OR luteinizing hormone OR LH OR estrogen OR testosterone OR LHRH OR gonadotropin-releasing hormone OR GnRH OR triptorelin OR GnRHa OR Gonadotropin-Releasing Hormone Agonist) AND (assay OR level OR test[tiab])) OR pelvic ultrasound OR gonadotropin-releasing hormone/blood[mh] OR (growth velocity AND puberty)	
Search 1 AND (2 OR 3) AND 4 Filters: published from 1990 onwards; Humans; English; NOT (case reports or case reports)		**766 (original) 80 (updated)**

Question 4

Search 1: Childhood cancer	((leukemia OR leukemi* OR leukaemi* OR (childhood ALL) OR AML OR lymphoma OR lymphom* OR hodgkin OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR sarcoma, Ewing's OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom*) OR (pediatric oncology OR paediatric oncology) OR (childhood cancer OR childhood tumor OR childhood tumors)) OR (brain tumor* OR brain tumour* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system tumor* OR central nervous system tumour* OR brain cancer* OR brain neoplasm* OR intracranial neoplasm*) OR (leukemia, lymphocytic, acute[mh])	
Search 2: Central hypocortisolism	((adrenocorticotropic hormone[mh] OR adrenocorticotropic hormone* OR ACTH OR hydrocortisone) AND (insufficiency OR deficiency)) OR ((adrenal OR hydrocortisone) AND (insufficiency OR deficiency OR crisis)) OR hypocortisolism OR hypocortisolism* OR Addison disease[mh]	
Search 3: Diagnostic test	Cortisol OR hydrocortisone OR ACTH OR adrenocorticotropic hormone OR morning glucose OR ITT OR insulin tolerance test[tiab] OR synacthen test[tiab] OR synacthen tests OR metyrapone	
Search 1 AND 2 AND 3 Filters: published from 1990 onwards; Humans; English; NOT (case reports or case reports)		**374 (original) 42 (updated)**

Question 4

Search 1: Childhood cancer	((leukemia OR leukemi* OR leukaemi* OR (childhood ALL) OR AML OR lymphoma OR lymphom* OR hodgkin OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR sarcoma, Ewing's OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom*) OR (pediatric oncology OR paediatric oncology) OR (childhood cancer OR childhood tumor OR childhood tumors)) OR (brain tumor* OR brain tumour* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system tumor* OR central nervous system tumour* OR brain cancer* OR brain neoplasm* OR intracranial neoplasm*) OR (leukemia, lymphocytic, acute[mh])
Search 2: Central hypocortisolism	((adrenocorticotropic hormone[mh] OR adrenocorticotropic hormone* OR ACTH OR hydrocortisone) AND (insufficiency OR deficiency)) OR ((adrenal OR hydrocortisone) AND (insufficiency OR deficiency OR crisis)) OR hypocortisolism OR hypocortisolism* OR Addison disease[mh]

Search 3: Steroids	dexamethasone OR dexamethasone* OR prednisone OR prednisone* OR prednisolone OR prednisolone* OR glucocorticoids OR glucocorticoid* OR "Steroids"[Mesh:NoExp] OR steroids*	
Search 1 AND 2 AND 3 Filters: published from 1990 onwards; Humans; English; NOT (case reports or case reports)		**194 (original) 18 (updated)**

Questions 6, 7 and 8 will be answered through expert opinion

Search strategies: WG4 "What should be done when abnormalities are identified?"

Question 1,2

Search 1: Childhood cancer	((leukemia OR leukemi* OR leukaemi* OR (childhood ALL) OR AML OR lymphoma OR lymphom* OR hodgkin OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR sarcoma, Ewing's OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom*) OR (pediatric oncology OR paediatric oncology) OR (childhood cancer OR childhood tumor OR childhood tumors)) OR (brain tumor* OR brain tumour* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system tumor* OR central nervous system tumour* OR brain cancer* OR brain neoplasm* OR intracranial neoplasm*) OR (leukemia, lymphocytic, acute[mh]) OR (leukemia, lymphocytic, acute*)	
Search 2: Survivors	(Survivor OR survivors OR survivor* OR long term survivor OR long term survivors OR long term survivor* OR survivo* OR surviving OR long term survival[tiab] OR survival[mh])	
Search 3: Late effects	("late effect" OR "late effects" OR "late effect*" OR "late side effect" OR "late side effects" OR "late side effect*" OR "late adverse effect" OR "late adverse effects" OR "late adverse effect*" OR long term effect[tiab] OR long term effect* OR long term adverse effects[mh] OR aftercare OR follow up studie* OR follow up study)	
Search 4: Growth hormone deficiency	(growth hormone OR GHD OR GH) AND (deficien* OR disorder OR impairment OR deviation)	
Search 5: Treatment	("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR treatment OR intervention*)	
Search 1 AND (2 OR 3) AND 4 AND 5 Filters: published from 1990 onwards; Humans; English; NOT (case report OR case reports)		**623 (original) 48 (updated)**

Question 1,2

Search 1: Childhood cancer	((leukemia OR leukemi* OR leukaemi* OR (childhood ALL) OR AML OR lymphoma OR lymphom* OR hodgkin OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR sarcoma, Ewing's OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom*) OR (pediatric oncology OR paediatric oncology) OR (childhood cancer OR childhood tumor OR childhood tumors)) OR (brain tumor* OR brain tumour* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system tumor* OR central nervous system tumour* OR brain cancer* OR brain neoplasm* OR intracranial neoplasm*) OR (leukemia, lymphocytic, acute[mh]) OR (leukemia, lymphocytic, acute*)	
Search 2: Survivors	(Survivor OR survivors OR survivor* OR long term survivor OR long term survivors OR long term survivor* OR survivo* OR surviving OR long term survival[tiab] OR survival[mh])	
Search 3: Late effects	("late effect" OR "late effects" OR "late effect*" OR "late side effect" OR "late side effects" OR "late side effect*" OR "late adverse effect" OR "late adverse effects" OR "late adverse effect*" OR long term effect[tiab] OR long term effect* OR long term adverse effects[mh] OR aftercare OR follow up studie* OR follow up study)	
Search 4: Central hypothyroidism	((Thyroid stimulation hormone OR TSH OR Thyrotropin releasing hormone OR TRH OR thyroxine OR tri iodothyronine OR triiodothyronine) AND (deficiency OR disease)) OR (thyroid hormones[mh] AND (deficiency OR disease)) OR thyroid diseas* OR hypothyroidism[mh] OR hypothyroidism* OR thyroxine OR levo-thyroxine OR tri-iodothyronine	
Search 5: Treatment	("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR treatment OR intervention*)	
Search 1 AND (2 OR 3) AND 4 AND 5 Filters: published from 1990 onwards; Humans; English; NOT (case report OR case reports)		**453 (original) 39 (updated)**

Question 1,2

Search 1: Childhood cancer	((leukemia OR leukemi* OR leukaemi* OR (childhood ALL) OR AML OR lymphoma OR lymphom* OR hodgkin OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR sarcoma, Ewing's OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom*) OR (pediatric oncology OR paediatric oncology) OR (childhood cancer OR childhood tumor OR childhood tumors)) OR (brain tumor* OR brain tumour* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system tumor* OR central nervous system tumour* OR brain cancer* OR brain neoplasm* OR intracranial neoplasm*) OR (leukemia, lymphocytic, acute[mh]) OR (leukemia, lymphocytic, acute*)	
Search 2: Survivors	(Survivor OR survivors OR survivor* OR long term survivor OR long term survivors OR long term survivor* OR survivo* OR surviving OR long term survival[tiab] OR survival[mh])	
Search 3: Late effects	("late effect" OR "late effects" OR "late effect*" OR "late side effect" OR "late side effects" OR "late side effect*" OR "late adverse effect" OR "late adverse effects" OR "late adverse effect*" OR long term effect[tiab] OR long term effect* OR long term adverse effects[mh] OR aftercare OR follow up studie* OR follow up study)	
Search 4: Central hypocortisolism	(((adrenocorticotropic hormone[mh] OR adrenocorticotropic hormone* OR ACTH OR hydrocortisone) AND (insufficiency OR deficiency)) OR ((adrenal OR hydrocortisone) AND (insufficiency OR deficiency OR crisis)) OR hypocortisolism OR hypocortisolism* OR Addison disease[mh])	
Search 5: Treatment	("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR treatment OR intervention*)	
Search 1 AND (2 OR 3) AND 4 AND 5 Filters: published from 1990 onwards; Humans; English; NOT (case report OR case reports)		**164 (original) 23 (updated)**

Question 1,2

Search 1: Childhood cancer	((leukemia OR leukemi* OR leukaemi* OR (childhood ALL) OR AML OR lymphoma OR lymphom* OR hodgkin OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR sarcoma, Ewing's OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom*) OR (pediatric oncology OR paediatric oncology) OR (childhood cancer OR childhood tumor OR childhood tumors)) OR (brain tumor* OR brain tumour* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system tumor* OR central nervous system tumour* OR brain cancer* OR brain neoplasm* OR intracranial neoplasm*) OR (leukemia, lymphocytic, acute[mh]) OR (leukemia, lymphocytic, acute*)	
Search 2: Survivors	(Survivor OR survivors OR survivor* OR long term survivor OR long term survivors OR long term survivor* OR survivo* OR surviving OR long term survival[tiab] OR survival[mh])	
Search 3: Late effects	("late effect" OR "late effects" OR "late effect*" OR "late side effect" OR "late side effects" OR "late side effect*" OR "late adverse effect" OR "late adverse effects" OR "late adverse effect*" OR long term effect[tiab] OR long term effect* OR long term adverse effects[mh] OR aftercare OR follow up studie* OR follow up study)	
Search 4: Hypogonadotropic hypogonadism	hypogonadotropic hypogonadism OR hypogonadism[mh] OR (infertility AND pituitary) OR ((follicle stimulating hormone OR FSH OR gonadotropin* OR luteinizing hormone OR LH OR estrogen OR testosterone) AND deficiency) OR ((puberty OR menarche OR sexual development) AND delay*) OR ((gonadotropin OR estrogen OR testosterone) AND (deficiency OR insufficiency))	
Search 5: Treatment	("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR treatment OR intervention*)	
Search 1 AND (2 OR 3) AND 4 AND 5 Filters: published from 1990 onwards; Humans; English; NOT (case report OR case reports)		**310 (original) 30 (updated)**

Question 1,2

Search 1: Childhood cancer	((leukemia OR leukemi* OR leukaemi* OR (childhood ALL) OR AML OR lymphoma OR lymphom* OR hodgkin OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR sarcoma, Ewing's OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom*) OR (pediatric oncology OR paediatric oncology) OR (childhood cancer OR childhood tumor OR childhood tumors)) OR (brain tumor* OR brain tumour* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system tumor* OR central nervous system tumour* OR brain cancer* OR brain neoplasm* OR intracranial neoplasm*) OR (leukemia, lymphocytic, acute[mh]) OR (leukemia, lymphocytic, acute*)	
Search 2: Survivors	(Survivor OR survivors OR survivor* OR long term survivor OR long term survivors OR long term survivor* OR survivo* OR surviving OR long term survival[tiab] OR survival[mh])	
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Search 4: Central Precocious puberty	((precocious AND (sexual OR puberty pubarche OR menarche)) OR CPP OR puberty, precocious[mh] OR premature puberty OR breast development puberty OR skeletal maturation OR epiphyseal plate closure OR bone age* OR skeletal age* OR thelarche)	
Search 5: Treatment	("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR treatment OR intervention*)	
Search 1 AND (2 OR 3) AND 4 AND 5 Filters: published from 1990 onwards; Humans; English; NOT (case report OR case reports)		**136 (original) 20 (updated)**

Inclusion criteria

Study population:

- Childhood, adolescent and young adult cancer survivors, diagnosed with cancer up to the age of 25 years (>75% of the population)
- Definition survivor: follow-up from end of tumor treatment onwards, or patients with stable residual disease (i.e. studies only describing the occurrence of HP dysfunction prior to cancer diagnosis or during treatment were excluded)
- Exclude: CAYA cancer survivors with craniopharyngioma or pituitary adenoma

Outcomes:

- Growth hormone deficiency (GH deficiency)
- Thyroid stimulating hormone deficiency (TSH deficiency)
- Luteinizing hormone/follicle stimulating hormone deficiency (LH/FSHD)
- Adrenocorticotropic hormone deficiency (ACTH deficiency)
- Central precocious puberty (CPP)

Types of studies

- All study designs, except for reviews, consensus statements, letters to the editor
- Longitudinal study design (either retrospective or prospective) with reported screenings protocol for HP dysfunction for WG2
- Sample size ≥20 patients for WG1
- Sample size ≥20 patients with HP dysfunction for WG2
- No restriction on the sample size for WG3. In addition, if the outcome was GHD, only studies reporting sensitivity, specificity, positive predictive values and/or negative predictive values. For TSHD, LH/FSHD, ACTHD and CPP, studies that assessed correlations between screenings modalities were included.
- Sample size ≥20 patients who received hormonal treatment for HP dysfunction for WG4 and reporting outcomes on either tumor recurrence or second neoplasms in CAYA cancer survivors with or without GH treatment.
- Multivariable analysis included for WG1

Strength of the recommendation (based on GRADE and modified AHA/ACC criteria)

Strong recommendation to do Benefits >>> risks & harms Using anchor term 'is recommended', and with low degree of uncertainty.
Moderate recommendation to do Benefits > or = risk & harms Using anchor term 'is reasonable', with higher degree of uncertainty; other factors such as personal values, clinical scenario and costs need to be considered in the decision making process.
Strong recommendation not to do No benefit / Potentially harm Using anchor term 'not recommended', and with low degree of uncertainty.

Abbreviations: AHA/ACC, American Heart Association/American College of Cardiology
Gibbons RJ, Smith S, Antman E. American College of Cardiology/American Heart Association clinical practice guidelines: Part I: where do they come from? Circulation. 2003; 107(23): 2979-86.

Grading of quality of evidence

Initial score based on type of evidence		
+4	Randomized controlled trials/systematic reviews of randomized controlled trials	
+2	Controlled clinical trials or observational evidence (e.g. cohort, case-control) for intervention questions	
+4	Observational evidence for etiologic, prognostic and diagnostic questions	
Factors	**Assessment**	**Effect on quality**
1. Study limitations	Risk of biased based on selection bias, attrition bias, detection bias and confounding	0 (no problems), -1 (problem with one element), -2 (problem with 2 elements), -3 (problem with three or more elements
2. Consistency of results	Degree of consistency of effect between or within studies	0 (all/most studies show similar results), -1 (lack of agreement between studies including statistical heterogeneity/conflicting results, e.g. effect sizes in different directions)
3. Directness of evidence	The generalizability of population and outcomes from each study to the population of interest	0 (population and outcomes broadly generalizable), -1 (problem with 1 element, e.g. population different from the defined inclusion criteria OR outcomes different from the defined inclusion, -2 (problem with 2 elements (population and outcomes)
4. Imprecision	The precision of the results	0 (no important imprecision when studies include many patients and many events and thus have narrow confidence intervals, -1 (important imprecision when studies include relatively few patients and few events and thus have wide confidence intervals OR if only one study has been identified) -2 (if there is important imprecision (see -1) AND if only one study has been identified
5. Publication bias	If investigators fail to report studies and outcomes (typically those that show no effect)	0 (publication bias unlikely), -1 (risk of publication bias when for example published evidence is limited to industry funded trials)
Increasing quality of evidence		
6. Magnitude of effect	-	**+1** (large magnitude of effect; all studies show significant effect sizes (point estimate) >2 or <0.5, +2 (very large magnitude of effect; all studies who significant effect sizes (point estimate) >5 or <0.2
7. Dose response gradient	-	**+1** (evidence of clear relation with increases in the outcome with higher exposure levels across or within studies
8. Plausible confounding	-	**+1** (if adjustment for confounders would have increased the effect size)
Total score		
⊕⊕⊕⊕	**High quality evidence**	
⊕⊕⊕⊖	**Moderate quality evidence**	
⊕⊕⊖⊖	**Low quality evidence**	
⊕⊖⊖⊖	**Very low quality evidence**	

10

Leydig cell function in male survivors of childhood cancer: a report from the St. Jude Lifetime Cohort Study

Wassim Chemaitilly, Qi Liu, Laura van Iersel, Kirsten K. Ness, Zhenghong Li, Carmen L. Wilson, Tara M. Brinkman, James L. Klosky, Nicole Barnes, Karen L. Clark, Rebecca M. Howell, Susan A. Smith, Matthew J. Krasin, Monika L. Metzger, Gregory T. Armstrong, Michael W. Bishop, Hanneke M. van Santen, Ching-Hon Pui, Deo .Kumar Srivastava, Yutaka Yasui, Melissa M. Hudson, Leslie L. Robison, Daniel M. Green, Charles A. Sklar

Submitted

Abstract

Context: Direct assessment of Leydig cell function in childhood cancer survivors has been limited.

Objectives: To describe the prevalence of, and risk factors for, Leydig cell failure (LCF) and associated adverse health outcomes.

Design: Retrospective cohort with cross-sectional health outcomes analysis.

Setting: The St. Jude Lifetime Cohort Study, an established cohort in a tertiary care center.

Patients: 1534 participants (median age 30.8 years) evaluated at a median of 22.0 years after cancer diagnosis.

Main Outcome Measure: LCF was defined as serum total testosterone <250 ng/dL (8.67 nmol/L) and LH >8.6 IU/L; compensated LCF by testosterone ≥250 ng/dL and LH >8.6 IU/L. Polytomous logistic regression evaluated associations with demographic and treatment-related risk factors. Log-binomial regression evaluated associations with adverse physical and psychosocial outcomes. Piecewise exponential models assessed the association with all-cause mortality.

Results: The prevalence of LCF and compensated LCF was 8.0% and 22.8%, respectively. Independent risk factors for LCF included age ≥36 years at assessment, testicular radiotherapy at any dose and alkylating agent chemotherapy at cyclophosphamide equivalent doses ≥4000 mg/m^2. LCF was statistically significantly associated with abdominal obesity, diabetes mellitus, erectile dysfunction, depression, frailty and mortality. For compensated LCF, the risk factor associations were similar to those for LCF; no significant associations were found with adverse physical or emotional outcomes.

Conclusion: Older age, testicular radiotherapy and alkylating agents were associated with LCF, which was associated with adverse physical and emotional outcomes. Further studies are needed to investigate the role of sex hormone replacement in mitigating such outcomes.

Introduction

Continued improvements in childhood cancer care have resulted in 5-year survival rates exceeding 80% in high-income countries.[1] In the United States, the population of childhood cancer survivors is expected to exceed 500,000 individuals by 2020.[2] Complications related to cancer and its treatments have nevertheless resulted in higher than expected rates of chronic health conditions[3], frail health[4] and all-cause mortality.[5] This has raised interest in modifiable risk factors, such as endocrine deficits, that may be contributing to adverse health outcomes in this population.[6]

Gonadal impairment is among the most common complications of cancer therapy.[7,8] Gonadal injury in childhood cancer survivors may result in decreased fertility and insufficient sex-hormone production.[9] In males, the testosterone producing compartment within the testes consists of Leydig cells, which are relatively quiescent when compared to the rapidly dividing reproductive germ cells, making them less vulnerable to damage from cancer therapies.[9] Leydig cell failure (LCF) has been reported in childhood cancer survivors exposed to gonadotoxic therapies such as testicular irradiation and alkylating agent chemotherapy[10-16], albeit less frequently than oligo/azoospermia.[8] The majority of affected individuals experience subclinical or compensated LCF with normal serum testosterone levels and elevated LH concentrations.[9,15,17]

Long-term follow-up data on LCF in childhood cancer survivors are scarce because the diagnosis requires direct clinical and laboratory evaluations and cannot be ascertained reliably through self-report.[14] Furthermore, assessment of the impact of LCF in adults requires the inclusion of psychosexual factors such as erectile dysfunction (ED), which are challenging to capture in cohorts of childhood cancer survivors.[18] Possible associations between elevated serum LH levels and decreased physical fitness in the general aging population[19,20], coupled with a growing concern regarding frailty in childhood cancer survivors[4], raise concerns regarding the impact of LCF and compensated LCF on long-term health outcomes and all-cause mortality after treatment for childhood cancer. We undertook this study to evaluate the prevalence of, and risk factors for, LCF and compensated LCF, as well as associated long-term adverse health outcomes in clinically evaluated childhood cancer survivors with extended follow-up.

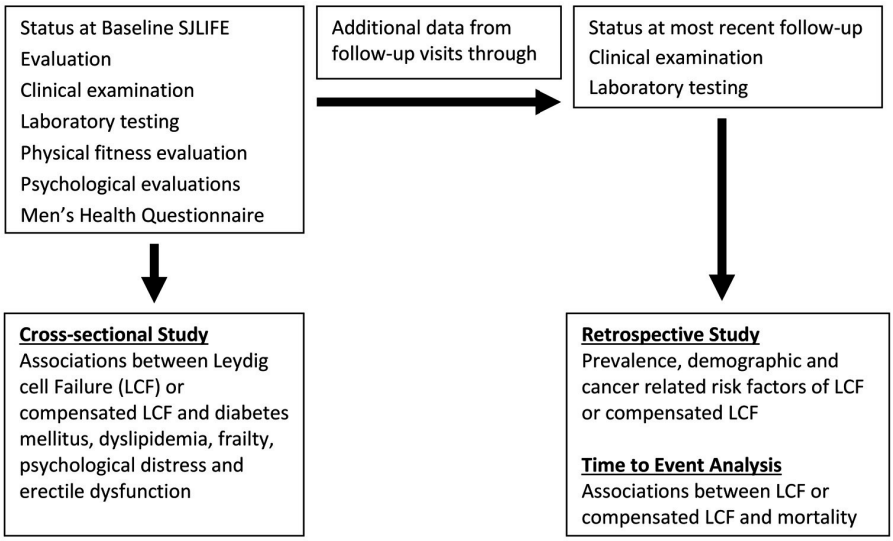
Patients and Methods

SJLIFE Study

Individuals were enrolled in the Institutional Review Board-approved SJLIFE Cohort Study. SJLIFE is a retrospective cohort study with prospective follow-up and ongoing data accrual. The detailed methods for ascertainment, recruitment and evaluation of this cohort of cancer survivors have been reported previously.[8,21-23] Participants eligible for the current analysis were male, ≥18 years of age and treated for childhood cancer at St. Jude Children's Research Hospital (SJCRH), with at

least five years of follow-up from cancer diagnosis. Eligible participants were invited to return to the SJCRH between 2007 and 2017 for a comprehensive baseline assessment that included a physical examination, standardized cardiopulmonary and neuromuscular performance testing, laboratory tests, and psychological evaluations. Medical, surgical, and cancer treatment history data were abstracted from medical records. Prior to the baseline clinical evaluation, participants were asked to complete questionnaires that assessed demographic, medical history, psychological, psychosexual, quality of life and behavioral health data. Follow-up visits, including clinical examination and laboratory testing were offered to all participants. Such subsequent visits have been completed for some participants, providing confirmatory endocrine assessments and additional clinical follow-up data (Figure 1).

Figure 1. Study design



Cancer Treatment Quantification

Radiation fields potentially impacting the testes included whole abdomen, inverted-Y, pelvis, prostate, bladder, testes, iliac, femoral and inguinal as well as total lymphoid or body irradiation. Doses absorbed by the testes were based on prescribed doses for direct exposures. For indirect exposures, testicular doses were estimated using radiation oncology treatment records as previously described.[24] Cumulative treatment exposure for alkylating agents was abstracted from the medical records and quantified using the cyclophosphamide equivalent dose (CED).[25]

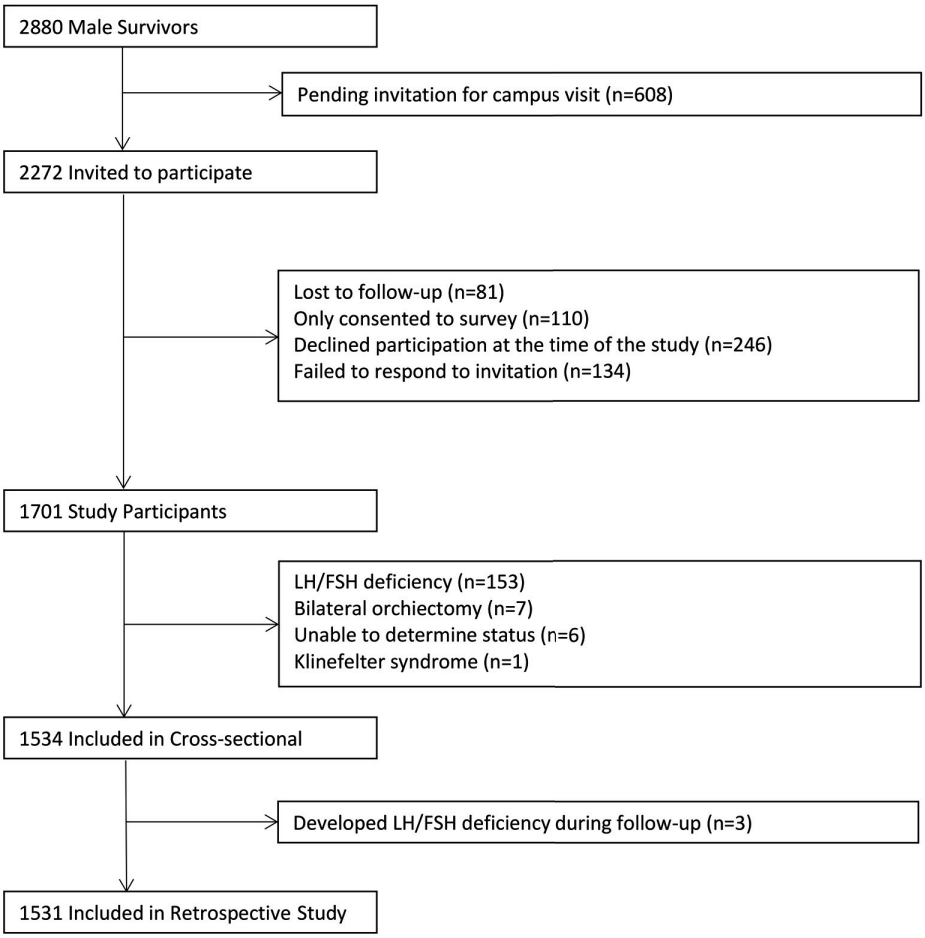
Diagnosis of LCF and Compensated LCF

For individuals not receiving sex-hormone replacement therapy, LCF was defined as morning serum levels of total testosterone <250 ng/dL (or 8.67 nmol/L) and LH >8.6 IU/L, and compensated LCF by testosterone ≥250 ng/dL and LH >8.6 IU/L. Testosterone and LH were measured using electro-chemiluminescent immunometric assay (Roche Cobas 6000 Analyzer; Roche Diagnostics, Indianapolis, IN). Normal values were based on data from the laboratory test manufacturer. For verification, morning serum testosterone and LH levels were independently measured at SJCRH on a sample of 168 non-cancer local population controls who were not on testosterone therapy (ages 18.3-62.7 years); a serum testosterone value of 250 mg/mL was between the 5th and 10th percentiles, and LH of 8.6 IU/L between the 90th and the 95th percentiles in the overall control sample (Supplemental Table 1). Individuals with multiple serum testosterone levels available who experienced a spontaneous normalization of testosterone levels at the most recent assessment were considered not to have had LCF at any time during follow-up.[26] Treatment with testosterone replacement was not interrupted in participants with a previously established and documented diagnosis of LCF. Individuals with morning serum total testosterone <250 ng/dL and LH ≤ 8.6 IU/L and those on testosterone replacement for a known diagnosis of LH/FSH deficiency due to hypothalamic/pituitary dysfunction (n=153) were excluded from the study as the status of their Leydig cell function could not be determined with certainty.[27] Individuals whose Leydig cell function status could not be determined based on historical information and laboratory results were also excluded from the study (n=6) (Figure 2).

Physical Health Outcomes

All participants had measurements of height, weight, and waist circumference. Body mass index (BMI) was calculated as weight (kilograms)/ height (meters)^2. Waist circumference ≥102 cm was considered indicative of abdominal obesity.[28] Fasting serum glucose, cholesterol, triglycerides, and high-density lipoproteins were measured using an enzymatic spectrophotometric assay (Roche Modular P Chemistry Analyzer; Roche Diagnostics). Diabetes mellitus was defined by a fasting serum glucose ≥126 mg/dL and/or treatment with glucose-lowering medications. Total cholesterol ≥200 mg/dL, low-density lipoprotein ≥130 mg/dL, high-density lipoprotein less than 40 mg/dL and/or triglycerides ≥150 mg/dL were used to define dyslipidemia.[29] Bone mineral density (BMD) was measured using quantitative computed tomography with GE VCT LightSpeed 64-detector (GE Healthcare, Waukesha, WI) and Mindways quantitative computed tomography calibration phantoms and software (Mindways, Austin, TX). Age- and sex-specific z-scores were calculated and used to report on average volumetric trabecular BMD for lumbar vertebrae L1 and L2; severe BMD deficit was defined as a z-score <-2.

Figure 2. Flow diagram



Physiologic frailty, a phenotype associated with accelerated aging and mortality[4,27] was defined by the presence of three or more of the following factors: low muscle mass, self-reported exhaustion, low energy expenditure, slow walking speed and muscle weakness.[30] Appendicular mass (kg) measured by dual x-ray absorptiometry and divided by height (m) squared was used to assess participants for low muscle mass, defined as values at least 1.5 standard deviations below age- and sex specific reference values.[31] Exhaustion was self-reported using the Vitality Subscale of the Medical Outcomes Survey Short Form-36; scores 1.3 standard deviations below the population mean were deemed consistent with exhaustion.[32] Energy expenditure was calculated using the National Health and Nutrition Survey Physical Activity Questionnaire and low energy expenditure was defined by values <383 kcal/week.[33] The time to cover a distance of 15 feet after

adjustment for height was used to assess for walking speed; values ≥7 seconds and ≥6 seconds were considered slow in individuals with heights <173 cm and ≥173 cm, respectively.[30] Hand grip strength (kg) was measured using a Jamar dynamometer (Preston Sammons, Nottinghamshire, United Kingdom), and weakness was classified by sex- and BMI-specific cut points.[30]

Erectile Dysfunction and Psychological Distress Parameters

ED was assessed in participants who completed a questionnaire evaluating male sexual health (n=892).[21] In sexually active participants, defined as having had some form of sexual activity with a partner over the preceding four weeks, mild to severe ED was defined by scores ≤25 using the validated 6-item version of the International Index of Erectile Function (IIEF).[34] In non-sexually active participants, responses to additional items querying problems getting or sustaining an erection were used to characterize ED.[18] Psychological distress was measured by the Brief Symptom Inventory-18 (BSI-18) questionnaire that provides a global measure of psychological distress, as well as subscales for anxiety, depression and somatization.[35]

Statistical analysis

The study design incorporated two separate analyses (Figure 1). The prevalence of LCF and compensated LCF and their associations with demographic and cancer treatment factors were assessed using the status at the most recent SJLIFE evaluation. Unadjusted associations of the outcome expressed as three mutually exclusive categories (LCF, compensated LCF, and neither) were assessed using polytomous logistic regression models including race/ethnicity, age at cancer diagnosis, age at first exposure to testicular radiotherapy or to alkylating agents, BMI, heavy drinking, cigarette smoking, illicit drug use, testicular radiotherapy dose and CED. Variable categorizations were primarily based on clinical relevance, but also considered statistical power to ensure that adequate numbers were available in each group. Variables with $p \leq 0.10$ from the unadjusted analysis entered the multivariable analysis. Association results are presented with estimated adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs).

Associations of LCF or compensated LCF with diabetes mellitus, dyslipidemia, abdominal obesity, severe BMD deficit, frailty, ED and psychological distress were examined in a cross-sectional fashion using participant LCF/compensated LCF status at the time of the SJLIFE baseline evaluation, when physical and psychosocial assessments were systematically and synchronously made (Figure 1). Individuals with laboratory values suggestive of LCF or compensated LCF at baseline and whose levels spontaneously normalized at the last follow-up were considered as having normal Leydig cell function for this analysis. Covariates in this analysis included race/ethnicity, age at cancer diagnosis, age at first exposure to testicular radiotherapy or to alkylating agents, BMI (except for the abdominal obesity outcome), heavy drinking, cigarette smoking, illicit drug use, testicular radiotherapy dose and CED. Covariates with $p \leq 0.10$ from the unadjusted

analysis for any of the outcomes were entered in multivariable models and were adjusted using the propensity score method with polytomous logistic models.[36] Log-binomial regression was used to estimate the adjusted prevalence ratios (PR) and 95% CIs. A time-to-event sub-analysis was conducted to examine the association of LCF or compensated LCF with subsequent all-cause mortality adjusting for the same set of covariates; a piecewise exponential model was used to estimate the adjusted rate ratios and 95% CIs.

Results

Point Prevalence of LCF and Compensated LCF

Of 2880 potentially-eligible male survivors, 2272 had been invited to participate in SJLIFE, of whom 1701 (75%) completed a clinical assessment. A total of 167 were excluded due to LH/FSH deficiency (n=153), a history of bilateral orchiectomy (n=7), a diagnosis of Klinefelter syndrome (n=1) or the status of their Leydig cell function could not be determined (n=6) (Fig. 2). Compared to nonparticipants, participants were less likely to have a diagnosis of a central nervous system (CNS) tumor, less likely to belong to an ethnic/racial minority group, and more likely to have been exposed to a higher CED (Table 1).

Laboratory data from the baseline evaluation were available on all 1534 study participants (median age 30.8 years; range 18.1-63.8) after a median of 22.0 years (range 7.5-49.8) and a mean 23.3 ±8.3 years since cancer diagnosis. At the baseline evaluation, 120 participants (7.8%, 95% CI: 6.5%-9.3%) had LCF and 304 (19.8%, 95% CI: 17.9%-21.9%) compensated LCF. Laboratory data from follow-up visits were available on 692 participants (45.1%) prospectively followed in SJLIFE over a median 4.8 years (range 0.8-7.6 years) (Figure 1). At subsequent SJLIFE evaluation, three participants developed LH/FSH deficiency (and were excluded from the risk factor analysis), one participant developed LCF, and 46 participants developed compensated LCF. In addition, one individual with compensated LCF at the baseline evaluation developed LCF with additional follow-up. One individual had baseline labs suggestive of compensated LCF but these became subsequently normal without treatment; there were no individuals with baseline labs suggestive of LCF and whose status changed with additional follow-up. The point prevalence of LCF and compensated LCF based on the most recent SJLIFE evaluation was 8.0% (95% CI 6.7%-9.4%) and 22.8% (95% CI: 20.7%-25.0%), respectively. Among a total of 122 individuals with LCF, 43 were receiving therapy with testosterone at the time of their most recent assessment (35.2%).

Risk Factors of LCF and Compensated LCF

The multivariable analysis showed that the risk for LCF was significantly higher in individuals aged 36-45.9 years (OR 4.0, 95% CI 1.8-8.6) or ≥46 years (OR 5.1, 95% CI 2.1-12.2) than in those 18-25 years old at the time of study (Table 2). Obese individuals (BMI ≥30 kg/m^2) were more likely to

have LCF (OR 2.3, 95% CI 1.3-4.1) than those with normal BMI (18.5-24.9 kg/m^2). Treatment-related risk factors for LCF included testicular radiotherapy at doses >0-11.9 (OR 3.0, 95% CI 1.3-6.7), 12-19.9 Gy (OR 87.5, 95% CI 26.6-288.2) or ≥20 Gy (OR∞, 95% CI 83.1-∞, all 19 survivors in >20 Gy had LCF) as well as treatment with alkylating agents at CED 4000-7999 mg/m^2 (OR 3.8, 95% CI 2.0-7.3), 8000-11999 mg/m^2 (OR 3.8, 95% CI 1.9-7.5) or ≥ 12000 mg/m^2 (OR 8.0, 95% CI 4.2-15.2).

The risk of compensated LCF was significantly higher in individuals aged 5-9.9 years (OR 1.5, 95% CI 1.1-2.2) compared to those aged 0-4.9 years at the time of cancer diagnosis (Table 2). Compensated LCF was more likely to occur in individuals aged 26-35.9 years (OR 1.5, 95 CI 1.0-2.21), 36-45.9 years (OR 1.7, 95% CI 1.1-2.7) or ≥46 years (OR 2.4, 95% CI 1.4-3.9) than in those 18-25 years old at the time of study. The risk of compensated LCF was higher in non-Hispanic Black participants (OR 1.7, 95% CI 1.1-2.4) than in non-Hispanic Whites. Obese individuals were less likely to have compensated LCF (OR 0.6, 95% CI 0.4-0.9) than those with normal BMI. Treatment-related risk factors for compensated LCF included testicular radiotherapy at doses >0-11.9 (OR 2.1, 95% CI 1.1-3.9), 12-19.9 Gy (OR 11.8, 95% CI 4.1-33.3) or ≥20 Gy (OR∞, 95% CI 5.5-∞, all 6 survivors in >20 Gy had compensated LCF) as well as treatment with alkylating agents at CED 4000-7999 mg/m^2 (OR 3.0, 95% CI 2.0-4.4), 8000-11999 mg/m^2 (OR 3.9, 95% CI 2.7-5.8) or ≥12000 mg/m^2 (OR 7.4, 95% CI 5.0-11.0) (Table 2).

Table 1. Participant and nonparticipant demographic and treatment characteristics

	Participants, N=1534		Nonparticipants, N=1346		p-value
	No.	%	No.	%	
Age at SJLIFE Participation					Not applicable
18-25.9 years	454	29.6	-	-	
26-35.9 years	632	41.2	-	-	
36-45.9 years	335	21.8	-	-	
46-55.9 years	99	6.5	-	-	
≥60 years	14	0.9	-	-	
Mean ±Standard Deviation	31.9±8.6		-	-	
Race/Ethnicity					0.20
Non-Hispanic White	1274	83.1	1076	79.9	
Non-Hispanic Black	210	13.7	216	16.0	
Hispanic	28	1.8	31	2.3	
Other	22	1.4	23	1.7	
Cancer Diagnosis					<0.001
Leukemia	530	34.6	424	31.5	
Lymphoma	340	22.1	282	21.0	

Table 1. Continued

	Participants, N=1534		Nonparticipants, N=1346		p-value
	No.	%	No.	%	
Bone and soft tissue sarcomas	225	14.7	169	12.6	
Wilms tumor	86	5.6	64	4.8	
CNS tumor	149	9.7	216	16.0	
Neuroblastoma	69	4.5	52	3.9	
Retinoblastoma	45	2.9	41	3.0	
Carcinomas	23	1.5	17	1.3	
Germ cell tumor	20	1.3	24	1.8	
Other	47	3.1	57	4.2	
Age at Cancer Diagnosis (years)					0.56
0 – 4.9	549	35.8	459	34.1	
5 – 9.9	361	23.5	337	25.0	
10 – 14.9	350	22.8	294	21.8	
≥15 years	274	17.9	256	19.0	
Testicular Irradiation Dose (Gy)					0.31
None	1388	90.5	1024	76.1	
>0 and 11.9	66	4.3	42	3.1	
12-19.9	40	2.6	37	2.7	
≥20	19	1.2	22	1.6	
Missing	21	1.4	221	16.4	
Cyclophosphamide Equivalent Dose (mg/m^2)					<0.001
0	617	40.2	560	41.6	
> 0 to < 4000	135	8.8	176	13.1	
≥ 4000 to < 8000	273	17.8	225	16.7	
≥ 8000 to < 12000	249	16.2	162	12.0	
≥ 12000	256	16.7	214	15.9	
Missing	4	0.3	9	0.7	
Education Level					Not applicable
No High School or GED	144	9.4	-	-	
High School or GED	392	25.6	-	-	
Some college	420	27.4	-	-	
Bachelor's degree or higher	429	28.0	-	-	
Unknown	149	9.7	-	-	

Abbreviations: SJLIFE, St. Jude Lifetime Cohort Study; GED, General Educational Diploma (high school equivalency diploma

Table 2. Multivariable logistic regression model fits for Leydig cell failure (LCF) and compensated LCF

		LCF (n=122)					Compensated LCF (n=349)				
Characteristic	**N**	**n§**	**%**	**OR**	**95% CI**	**p**	**nµ**	**%**	**OR**	**95% CI**	**p**
Age at Diagnosis (years)											
0-4.9	548	37	6.8	1.0			104	19.0	1.0		
5-9.9	361	33	9.1	1.6	0.9 - 2.9	0.11	86	23.8	1.5	1.1 - 2.2	0.03
10-14.9	349	30	8.6	1.0	0.6 - 1.9	0.89	88	25.2	1.3	0.9 - 1.9	0.12
≥15	273	22	8.1	0.8	0.4 - 1.6	0.52	71	26.0	1.3	0.8 - 1.9	0.26
Age at Study (years)											
18-25.9	350	14	4.0	1.0			62	17.7	1.0		
26-35.9	617	40	6.5	2.1	1.0 - 4.5	0.05	137	22.2	1.5	1.0 - 2.2	0.04
36-45.9	374	45	12.0	4.0	1.8 - 8.6	<0.001	89	23.8	1.7	1.1 - 2.7	0.01
≥46	190	23	12.1	5.1	2.1 - 12.2	<0.001	61	32.1	2.4	1.4 - 3.9	<0.001
Race/Ethnicity											
Non-Hispanic White	1272	100	7.9	1.0			277	21.8	1.0		
Non-Hispanic Black	209	17	8.1	1.6	0.8 - 3.0	0.15	57	27.3	1.7	1.1 - 2.4	0.01
Other	50	5	10.0	1.4	0.5 - 4.4	0.54	15	30.0	1.2	0.6 - 2.6	0.57
Body Mass Index (kg/m^2)											
≥ 18.5- 24.9	480	24	5.0	1.0			128	26.7	1.0		
<18.5	41	2	4.9	1.2	0.2 - 5.8	0.85	19	46.3	1.7	0.8 - 3.7	0.16
25-29.9	506	39	7.7	1.3	0.7 - 2.4	0.38	114	22.5	0.7	0.5 - 1.0	0.07
≥ 30	490	55	11.2	2.3	1.3 - 4.1	0.01	83	16.9	0.6	0.4 - 0.9	0.01

Table 2. Continued

		LCF (n=122)					Compensated LCF (n=349)				
Characteristic	**N**	**n§**	**%**	**OR**	**95% CI**	**p**	**nμ**	**%**	**OR**	**95% CI**	**p**
Testicular Radiation Dose (Gy)											
None	1386	80	5.8	1.0			298	21.5	1.0		
>0 – 11.9	65	10	15.4	3.0	1.3 - 6.7	0.01	24	36.9	2.1	1.1 - 3.9	0.02
12-19.9	40	17	42.5	87.5	26.6 - 288.2	<0.001	16	40.0	11.8	4.1 - 33.3	<0.001
≥ 20	19	13	68.4	∞	83.1-∞	<0.001	6	31.6	∞	5.5-∞	<0.001
CED (mg/m^2)											
0	616	20	3.2	1.0			69	11.2	1.0		
> 0 - < 4000	135	12	8.9	0.7	0.3 - 2.0	0.57	22	16.3	1.0	0.5 - 1.8	0.91
4000 - < 8000	273	27	9.9	3.8	2.0 - 7.3	<0.001	70	25.6	3.0	2.0 - 4.4	<0.001
8000 - < 12000	248	22	8.9	3.8	1.9 - 7.5	<0.001	77	31.0	3.9	2.7 - 5.8	<0.001
≥ 12000	255	40	15.7	8.0	4.2 - 15.2	<0.001	109	42.7	7.4	5.0 - 11.0	<0.001

Abbreviations: CED, Cyclophosphamide Equivalent Dose; §, number of patients with LCF with each characteristic; μ, number of patients with compensated LCF with each characteristic

Associations between LCF/compensated LCF and Chronic Health Conditions or All-Cause Mortality

The multivariable cross-sectional analysis showed significant associations between LCF and increased waist circumference (PR 1.6, 95%CI 1.2-2.0), diabetes mellitus (PR 2.4, 95% CI 1.5-4.0), ED (PR 1.8, 95% CI 1.4-2.4), frailty (PR 2.5, 95%CI 1.2-5.0), and depression (PR 1.5, 95% CI 1.0-2.1) after adjustment for other potentially contributing risk factors (Table 3). Subsequent all-cause mortality was also independently associated with the baseline status of LCF (PR 4.5; 95% CI 2.1-9.50; p <0.001). Individuals with increased waist circumference were less likely to have compensated LCF (PR 0.7, 95% CI 0.50-0.90); no associations were otherwise found between compensated LCF and adverse chronic health outcomes (p >0.05; Table 3).

To evaluate the effect of testosterone replacement on health outcomes measures in individuals with LCF, we repeated the analysis by separating treated and untreated LCF at the time of the evaluation. After adjustment for potential confounders, untreated LCF maintained the same independent associations as those described above for LCF overall except for depression, which became insignificant (Table 4). Treated LCF remained associated with increased waist circumference (PR 1.6, 95% CI 1.0-2.4), ED (PR 1.8, 95% CI 1.1-2.8) and depression (PR 2.0, 95% CI 1.2-3.3) but not with diabetes mellitus, frailty or all-cause mortality (Table 4).

Table 3. Multivariable regression model fits for Leydig cell failure (LCF), compensated LCF, physical and sexual health parameters

	No LCF or Compensated LCF	LCF				Compensated LCF			
		Present	Multivariable analysis			Present	Multivariable analysis		
Outcome variables	N (%)	N (%)	PR*	95% CI	p	N%	PR**	95% CI	p
Increased waist circumference	262 (23.8)	46 (39.3)	1.6	1.2 - 2.0	<0.001	46 (15.4)	0.7	0.5 - 0.9	0.004
Diabetes mellitus	50 (4.5)	22 (18.3)	2.5	1.5 - 4.0	<0.001	22 (7.2)	1.4	0.9 - 2.3	0.18
Erectile dysfunction	170 (26.4)	35 (50)	1.8	1.4 - 2.4	<0.001	52 (29.4)	1.1	0.8 - 1.4	0.70
Mortality[a]	27 (5.3)	12 (21.1)	4.5[b]	2.1 - 9.5	<0.001	17 (11.7)	1.5[b]	0.8 – 3.0	0.24
Frailty	31 (2.9)	11 (9.6)	2.4	1.2 - 5.0	0.02	8 (2.9)	0.8	0.4 - 1.7	0.54
Depression	169 (16.1)	29 (25.2)	1.5	1.0 - 2.1	0.04	42 (14.6)	0.9	0.6 - 1.2	0.44

PR (prevalence ratio) is calculated for *LCF yes vs no LCF/compensated LCF and **compensated LCF yes vs. no LCF/compensated LCF

Models adjusted for age at study, race/ethnicity, age at diagnosis, BMI (except for waist circumference), testicular radiotherapy, illicit drug use, and smoking status. [a] For the mortality outcome, the rate per 1000 person years is given instead of %. [b] Result for mortality is expressed as rate ratio

Table 4. Multivariable regression model fits for treated, untreated and compensated Leydig cell failure (LCF) and physical, psychological and sexual health parameters

	No LCF nor Compensated LCF	LCF Untreated				LCF Treated				Compensated LCF			
		Present	Multivariable analysis			Present	Multivariable analysis			Present	Multivariable analysis		
Outcome variables	N (%)	N (%)	PR*	95% CI	p		PR**	95% CI	p	N%	PR§	95% CI	p
Increased waist circum-ference	262 (23.8)	32 (41)	1.5	1.1 – 2.0	0.009	15 (35.9)	1.6	1.0 - 2.4	0.05	46 (15.4)	0.7	0.5 - 0.9	0.003
Diabetes mellitus	50 (4.5)	16 (19.8)	2.4	1.4 - 4.2	0.001	6 (15.4)	1.7	0.8 - 3.8	0.21	22 (7.2)	1.3	0.8 - 2.1	0.31
Erectile dysfunction	170 (26.4)	24 (52.2)	1.9	1.4 - 2.5	<0.001	11 (45.8)	1.8	1.1 - 2.8	0.02	52 (29.4)	1.1	0.8 - 1.4	0.68
Mortality [a]	27 (5.3)	10 (25.7)	4.7[b]	2.1 - 10.6	<0.001	2 (11.2)	4.7[b]	0.8 - 16.1	0.09	17 (11.7)	1.5	0.8 – 3.0	0.24
Frailty	31 (2.9)	8 (10.4)	2.7	1.2 - 6.1	0.01	3 (8.1)	2.1	0.6 - 7.1	0.22	8 (2.9)	0.8	0.4 - 1.7	0.50
Depression	169 (16.1)	17 (21.5)	1.3	0.8 - 2.0	0.35	12 (33.3)	2.0	1.2 - 3.3	0.01	42 (14.6)	0.9	0.6 - 1.2	0.37

PR (prevalence ratio) is calculated for *LCF yes vs no LCF/compensated LCF and **compensated LCF yes vs. no LCF/compensated LCF
Models adjusted for age at study, race/ethnicity, age at diagnosis, BMI (except for waist circumference), testicular radiotherapy, illicit drug use, and smoking status.
[a] For the mortality outcome, the rate per 1000 person years is given instead of %. [b] Result for mortality is expressed as rate ratio.

Discussion

In this large cohort of clinically assessed male survivors of childhood cancer, we identified significant long-term adverse physical and emotional health outcomes that were associated with cancer treatment-related LCF. LCF was independently associated with excess risk for remediable conditions known to predispose to cardiovascular disease, poor functional status, and impaired quality of life. Notably, LCF predicted an almost five-fold excess risk of mortality. Many of these significant adverse associations persisted among childhood cancer survivors with LCF who reported taking hormonal replacement therapy. Our study findings also extend previous knowledge regarding associations between LCF and treatment-related risk factors such as testicular radiotherapy and alkylating agents.[14]

There are few studies that report on the overall prevalence of LCF in childhood cancer survivors. Moreover, several of the published studies have reported on this outcome after short follow-up durations[37] or based on a single cross-sectional evaluation[14,38], while others do not make clear distinctions between LCF and germ cell failure and/or between primary and central causes of low testosterone.[12,39-41] These distinctions are, however, essential[42], especially in the context of cancer survivorship, given the differential vulnerability of Leydig cells and germ cells to cancer therapies, and the need to counsel and screen individuals based on their treatment exposures.[8,9] The prevalence of LCF in SJLIFE participants was within the range of 5.8%-10.8% previously reported by others.[14,37,38] LCF was substantially less frequent in childhood cancer survivors than oligo- or azoospermia, which have been previously reported in 25% and 28% of tested individuals, respectively.[43] The prevalence of compensated LCF in SJLIFE (22.8%) was similar to limited data (23.8%) inferred from the laboratory results reported by Greenfield and colleagues.[14] By comparison, the prevalence of LCF and compensated LCF in the general population reported in the European Male Ageing Study (2% and 9.5%, respectively), were strikingly lower than those reported in SJLIFE despite the substantially older age of their participants (mean 59.7±11 years vs. 31.9±8.9 years).[19]

The major risk factor for LCF in SJLIFE was exposure of the testis to radiotherapy, similar to what has been reported by others.[10-12,16,44] Doses of testicular radiotherapy ≥ 20 Gy have been shown to pose the greatest risk for LCF in childhood cancer survivors followed short-term.[11,44] While individuals treated with lower doses of testicular radiation appeared to enter and progress through puberty spontaneously, the long-term risk of LCF was generally not assessed.[11,44] The SJLIFE cohort findings demonstrate that, with longer follow-up, testicular radiotherapy doses < 20 Gy represent a significant risk factor for LCF. Testicular radiotherapy at any dose was also associated with compensated LCF, consistent with the findings of others.[45,46]

Data pertaining to the effect of alkylating agents on Leydig cell function have been reported primarily in studies of patients treated with chemotherapy alone for Hodgkin lymphoma, or conditioning for hematopoietic stem cell transplant. The evidence supporting an association between alkylating agents and LCF has historically been less convincing than data on the effect of radiotherapy with most studies reporting subclinical forms of LCF.[13,15,47,48] An association between higher cumulative doses of cyclophosphamide and elevated LH levels has also been observed.[47] The data from SJLIFE demonstrate, with a greater level of confidence, that treatment with alkylating agents at CED ≥4000 mg/m^2 represents an independent risk factor for both LCF and compensated LCF; the risk increases with increasing CED and is substantial at doses ≥12000 mg/m^2. In our study, 15.7% and 42.7% of individuals exposed to CED≥12000 mg/m^2 had LCF and compensated LCF, respectively. Therefore, the follow-up of childhood cancer survivors exposed to alkylating agents should include periodic evaluations of Leydig cell function via the measurement of morning testosterone and LH levels. In addition, these individuals should be counseled regarding their risk of both impaired testosterone production as well as the risk of infertility.[49]

Demographic and host factors also impact Leydig cell function in childhood cancer survivors. Older age at evaluation was significantly associated with LCF and compensated LCF. This finding highlights the nature of LCF as a late effect in childhood cancer survivors. Despite the known increase in the prevalence of LCF with aging in the non-cancer population[19,26], it is important to note the relatively young age of SJLIFE participants (median 32.7 years) and that the risk for LCF increases during the third decade of life in this cohort. Young age at treatment has previously been reported as an additional risk factor of radiation-induced LCF.[44,46] This association was found in SJLFE only for compensated LCF.

Obese SJLIFE participants had significantly higher rates of LCF than non-obese individuals. This is a surprising finding as BMI was incorporated in the risk factor analysis to adjust for the lower LH and testosterone levels often observed in obese individuals.[26,39] This finding, which implies a possible causal association between LCF and abnormal body composition, requires further investigation. In contrast, compensated LCF was significantly less common in obese participants, possibly because of the known association between obesity and lower LH levels.[26] The risk of compensated LCF was higher in non-Hispanic Black participants, a novel observation that requires validation in other cohorts. Data from non-cancer populations on correlations between ethnicity and LH are scarce with limited evidence supporting higher LH levels in individuals of African/Caribbean ancestry.[50]

The ability to examine associations between LCF, compensated LCF and adverse health outcomes is one of the main strengths of this study as few reports have specifically addressed these associations in childhood cancer survivors.[14,51] Understanding the health implications of LCF is

essential as these are important considerations for the initiation of replacement therapy.[26] Low testosterone in childhood cancer survivors was associated with increased body fat, impaired glucose tolerance, insulin resistance and decreased quality of life in a cross-sectional study of 176 childhood cancer survivors and 213 controls.[14] In a study comparing quality of life variables between the 51 male survivors of childhood acute lymphoblastic leukemia and 56 age-matched controls, exposure to CED ≤10000 mg/m^2 with or without testicular radiotherapy was associated with lower quality of life, impaired emotional well-being and decreased energy.[51] The findings of the SJLIFE cohort support an independent effect of LCF on impaired physical, emotional and sexual health parameters, which are consistent with the classic presentation of male hypogonadism in the non-cancer population.[26] As cancer survivors are more likely to develop associated co-morbidities, the adverse consequences of LCF may be even greater in this high-risk population.[8] The significant associations between LCF, frailty and all-cause mortality are concerning; however, the analysis does not allow us to speculate on causality, as older age and burden from chronic disease are known to be associated with elevated LH and low testosterone levels in the general population.[20,26,52] Interestingly, compensated LCF was not independently associated with any adverse health outcome.

Only a minority (35.2%) of SJLIFE participants with LCF were receiving exogenous testosterone at the time of the study, which may be related to lack of physician understanding of the global benefits of androgen therapy[26] or to challenges with accessing care.[8] The cross-sectional nature of the sub-analysis evaluating associations between chronic health outcomes and treated LCF and the small numbers of participants included do not allow definitive conclusions regarding the benefits or effects of treatment with exogenous testosterone. Significant associations between treated LCF, abdominal obesity, ED and depression may be indicative of factors driving testosterone prescription rather than due to a lack of response to therapy. Conversely, the absence of significant association between treated LCF, frailty and / or all-cause mortality could be reflective of the non-treatment of participants with significantly impaired physical condition rather than an indicator of the efficacy of testosterone replacement in mitigating these severe outcomes.

This study has several limitations that should be considered when interpreting our findings. Serial clinical and laboratory evaluations were available on only 45% of participants, while confirmatory data supporting the diagnosis of LCF on two separate occasions are recommended by the Endocrine Society.[26] Other limitations include the assumption that diagnoses of LCF prior to SJLIFE participation were accurate and permanent, the cross-sectional nature of the analysis of association with chronic health outcomes, the lack of standard diagnostic tools for ED in non-sexually active males and the need to retrospectively estimate testicular radiotherapy doses.

In summary, LCF and compensated LCF are not uncommon in childhood cancer survivors and can develop years after completion of cancer therapy. LCF is associated with adverse physical, psychological and psychosexual outcomes as well as mortality. Compensated LCF is more common than LCF but does not seem to be independently associated with adverse chronic health outcomes. The benefits and risks of replacement with exogenous testosterone in childhood cancer survivors with LCF require further study.

References

1. Jemal A, Ward EM, Johnson CJ, et al. Annual Report to the Nation on the Status of Cancer, 1975-2014, Featuring Survival. *J Natl Cancer Inst.* 2017;109(9).
2. Robison LL, Hudson MM. Survivors of childhood and adolescent cancer: life-long risks and responsibilities. *Nat Rev Cancer.* 2014;14(1):61-70.
3. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med.* 2006;355(15):1572-1582.
4. Ness KK, Krull KR, Jones KE, et al. Physiologic frailty as a sign of accelerated aging among adult survivors of childhood cancer: a report from the St Jude Lifetime cohort study. *J Clin Oncol.* 2013;31(36):4496-4503.
5. Armstrong GT, Kawashima T, Leisenring W, et al. Aging and risk of severe, disabling, life-threatening, and fatal events in the childhood cancer survivor study. *J Clin Oncol.* 2014;32(12):1218-1227.
6. Wilson CL, Chemaitilly W, Jones KE, et al. Modifiable Factors Associated With Aging Phenotypes Among Adult Survivors of Childhood Acute Lymphoblastic Leukemia. *J Clin Oncol.* 2016;34(21):2509-2515.
7. Brignardello E, Felicetti F, Castiglione A, et al. Endocrine health conditions in adult survivors of childhood cancer: the need for specialized adult-focused follow-up clinics. *Eur J Endocrinol.* 2013;168(3):465-472.
8. Hudson MM, Ness KK, Gurney JG, et al. Clinical ascertainment of health outcomes among adults treated for childhood cancer. *JAMA.* 2013;309(22):2371-2381.
9. Sklar C. Reproductive physiology and treatment-related loss of sex hormone production. *Med Pediatr Oncol.* 1999;33(1):2-8.
10. Brauner R, Czernichow P, Cramer P, Schaison G, Rappaport R. Leydig-cell function in children after direct testicular irradiation for acute lymphoblastic leukemia. *N Engl J Med.* 1983;309(1):25-28.
11. Sklar CA, Robison LL, Nesbit ME, et al. Effects of radiation on testicular function in long-term survivors of childhood acute lymphoblastic leukemia: a report from the Children Cancer Study Group. *J Clin Oncol.* 1990;8(12):1981-1987.
12. Romerius P, Stahl O, Moell C, et al. Hypogonadism risk in men treated for childhood cancer. *J Clin Endocrinol Metab.* 2009;94(11):4180-4186.
13. Mackie EJ, Radford M, Shalet SM. Gonadal function following chemotherapy for childhood Hodgkin's disease. *Med Pediatr Oncol.* 1996;27(2):74-78.
14. Greenfield DM, Walters SJ, Coleman RE, et al. Prevalence and consequences of androgen deficiency in young male cancer survivors in a controlled cross-sectional study. *J Clin Endocrinol Metab.* 2007;92(9):3476-3482.
15. Howell SJ, Radford JA, Ryder WD, Shalet SM. Testicular function after cytotoxic chemotherapy: evidence of Leydig cell insufficiency. *J Clin Oncol.* 1999;17(5):1493-1498.
16. Shalet SM, Horner A, Ahmed SR, Morris-Jones PH. Leydig cell damage after testicular irradiation for lymphoblastic leukaemia. *Med Pediatr Oncol.* 1985;13(2):65-68.
17. Afify Z, Shaw PJ, Clavano-Harding A, Cowell CT. Growth and endocrine function in children with acute myeloid leukaemia after bone marrow transplantation using busulfan/cyclophosphamide. *Bone Marrow Transplant.* 2000;25(10):1087-1092.
18. van Iersel L, Li Z, Chemaitilly W, et al. Erectile Dysfunction in Male Survivors of Childhood Cancer. *JAMA Oncol.* 2018;4(11):1613-1616.
19. Tajar A, Forti G, O'Neill TW, et al. Characteristics of secondary, primary, and compensated hypogonadism in aging men: evidence from the European Male Ageing Study. *J Clin Endocrinol Metab.* 2010;95(4):1810-1818.

20. van den Beld A, Huhtaniemi IT, Pettersson KS, et al. Luteinizing hormone and different genetic variants, as indicators of frailty in healthy elderly men. *J Clin Endocrinol Metab.* 1999;84(4):1334-1339.

21. Hudson MM, Ness KK, Nolan VG, et al. Prospective medical assessment of adults surviving childhood cancer: study design, cohort characteristics, and feasibility of the St. Jude Lifetime Cohort study. *Pediatr Blood Cancer.* 2011;56(5):825-836.

22. Hudson MM, Ehrhardt MJ, Bhakta N, et al. Approach for Classification and Severity Grading of Long-term and Late-Onset Health Events among Childhood Cancer Survivors in the St. Jude Lifetime Cohort. *Cancer Epidemiol Biomarkers Prev.* 2017;26(5):666-674.

23. Ojha RP, Oancea SC, Ness KK, et al. Assessment of potential bias from non-participation in a dynamic clinical cohort of long-term childhood cancer survivors: results from the St. Jude Lifetime Cohort Study. *Pediatr Blood Cancer.* 2013;60(5):856-864.

24. Stovall M, Weathers R, Kasper C, et al. Dose reconstruction for therapeutic and diagnostic radiation exposures: use in epidemiological studies. *Radiat Res.* 2006;166(1 Pt 2):141-157.

25. Green DM, Nolan VG, Goodman PJ, et al. The cyclophosphamide equivalent dose as an approach for quantifying alkylating agent exposure: a report from the Childhood Cancer Survivor Study. *Pediatr Blood Cancer.* 2014;61(1):53-67.

26. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2018;103(5):1715-1744.

27. Chemaitilly W, Li Z, Huang S, et al. Anterior hypopituitarism in adult survivors of childhood cancers treated with cranial radiotherapy: a report from the st jude lifetime cohort study. *J Clin Oncol.* 2015;33(5):492-500.

28. World Health Organization. *Obesity : preventing and managing the global epidemic : report of a WHO consultation*. Geneva: World Health Organization; 2000.

29. National Cholesterol Education Program Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation.* 2002;106(25):3143-3421.

30. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci.* 2001;56(3):M146-156.

31. Kelly TL, Wilson KE, Heymsfield SB. Dual energy X-Ray absorptiometry body composition reference values from NHANES. *PLoS One.* 2009;4(9):e7038.

32. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care.* 1992;30(6):473-483.

33. Ainsworth BE, Haskell WL, Herrmann SD, et al. 2011 Compendium of Physical Activities: a second update of codes and MET values. *Med Sci Sports Exerc.* 2011;43(8):1575-1581.

34. Cappelleri JC, Rosen RC, Smith MD, Mishra A, Osterloh IH. Diagnostic evaluation of the erectile function domain of the International Index of Erectile Function. *Urology.* 1999;54(2):346-351.

35. Recklitis CJ, Parsons SK, Shih MC, Mertens A, Robison LL, Zeltzer L. Factor structure of the brief symptom inventory--18 in adult survivors of childhood cancer: results from the childhood cancer survivor study. *Psychol Assess.* 2006;18(1):22-32.

36. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika.* 1983; 70:41–55.

37. Brignardello E, Felicetti F, Castiglione A, et al. Gonadal status in long-term male survivors of childhood cancer. *J Cancer Res Clin Oncol.* 2016;142(5):1127-1132.

38. Isaksson S, Bogefors K, Stahl O, et al. High risk of hypogonadism in young male cancer survivors. *Clin Endocrinol (Oxf).* 2018;88(3):432-441.

39. Relander T, Cavallin-Stahl E, Garwicz S, Olsson AM, Willen M. Gonadal and sexual function in men treated for childhood cancer. *Med Pediatr Oncol.* 2000;35(1):52-63.
40. Siimes MA, Rautonen J, Makipernaa A, Sipila I. Testicular function in adult males surviving childhood malignancy. *Pediatr Hematol Oncol.* 1995;12(3):231-241.
41. de Fine LS, Winther JF, Gudmundsdottir T, et al. Hospital contacts for endocrine disorders in Adult Life after Childhood Cancer in Scandinavia (ALiCCS): a population-based cohort study. *Lancet.* 2014;383(9933):1981-1989.
42. Rey RA, Grinspon RP, Gottlieb S, et al. Male hypogonadism: an extended classification based on a developmental, endocrine physiology-based approach. *Andrology.* 2013;1(1):3-16.
43. Green DM, Liu W, Kutteh WH, et al. Cumulative alkylating agent exposure and semen parameters in adult survivors of childhood cancer: a report from the St Jude Lifetime Cohort Study. *Lancet Oncol.* 2014;15(11):1215-1223.
44. Leiper AD, Grant DB, Chessells JM. Gonadal function after testicular radiation for acute lymphoblastic leukaemia. *Arch Dis Child.* 1986;61(1):53-56.
45. Sarafoglou K, Boulad F, Gillio A, Sklar C. Gonadal function after bone marrow transplantation for acute leukemia during childhood. *J Pediatr.* 1997;130(2):210-216.
46. Shalet SM, Tsatsoulis A, Whitehead E, Read G. Vulnerability of the human Leydig cell to radiation damage is dependent upon age. *J Endocrinol.* 1989;120(1):161-165.
47. Bramswig JH, Heimes U, Heiermann E, Schlegel W, Nieschlag E, Schellong G. The effects of different cumulative doses of chemotherapy on testicular function. Results in 75 patients treated for Hodgkin's disease during childhood or adolescence. *Cancer.* 1990;65(6):1298-1302.
48. Heikens J, Behrendt H, Adriaanse R, Berghout A. Irreversible gonadal damage in male survivors of pediatric Hodgkin's disease. *Cancer.* 1996;78(9):2020-2024.
49. Kenney LB, Cohen LE, Shnorhavorian M, et al. Male reproductive health after childhood, adolescent, and young adult cancers: a report from the Children's Oncology Group. *J Clin Oncol.* 2012;30(27):3408-3416.
50. Eendebak RJ, Swiecicka A, Gromski PS, et al. Ethnic differences in male reproductive hormones and relationships with adiposity and insulin resistance in older men. *Clin Endocrinol (Oxf).* 2017;86(5):660-668.
51. Gunn ME, Lahteenmaki PM, Puukko-Viertomies LR, Henriksson M, Heikkinen R, Jahnukainen K. Potential gonadotoxicity of treatment in relation to quality of life and mental well-being of male survivors of childhood acute lymphoblastic leukemia. *J Cancer Surviv.* 2013;7(3):404-412.
52. Tajar A, O'Connell MD, Mitnitski AB, et al. Frailty in relation to variations in hormone levels of the hypothalamic-pituitary-testicular axis in older men: results from the European male aging study. *J Am Geriatr Soc.* 2011;59(5):814-821.

Supplementary material

Supplemental Table 1. Age-adjusted LH levels and testosterone in SJLIFE local population controls

		LH, IU/L					Total testosterone, ng/dl				
Per-centile	Age (n)	18-29 (61)	30-39 (59)	40-49 (36)	≥50 (12)	Overall	18-29 (61)	30-39 (59)	40-49 (36)	≥50 (12)	Overall
0		1.71	1.78	1.84	3.43	1.71	264	95	171	167	95
5		2.39	2.19	2.03	3.43	2.19	317	189	225	167	**210**
10		3.11	2.54	2.19	3.50	2.71	347	210	236	211	**251**
15		3.59	2.84	2.73	3.50	3.10	399	255	240	211	285
20		3.89	3.20	3.06	3.59	3.44	414	303	282	299	319
25		3.95	3.46	3.2	3.59	3.62	428	328	282	299	348
30		4.05	3.93	3.52	4.31	3.92	449	368	298	465	380
35		4.53	4.00	3.54	4.31	4.02	476	388	313	465	408
40		4.68	4.16	3.74	4.34	4.24	501	414	320	518	421
45		4.93	4.37	3.80	4.34	4.48	513	420	345	518	438
50		5.13	4.52	4.02	4.85	4.67	539	432	355	518	470
55		5.26	4.93	4.35	5.29	4.97	568	472	376	547	497
60		5.40	5.08	4.48	5.29	5.21	597	479	392	547	572
65		5.53	5.28	4.59	6.11	5.37	608	520	508	564	548
70		5.91	5.43	5.03	6.11	5.69	616	571	423	564	588
75		6.10	5.71	6.43	7.61	6.09	637	593	439	766	609
80		6.50	5.98	6.50	7.61	6.48	688	621	468	766	635
85		7.96	6.49	6.79	8.67	6.79	698	667	543	832	689
90		8.45	6.78	7.20	8.67	**7.66**	740	797	629	832	736
95		9.85	7.45	7.48	10.95	**8.92**	835	851	657	938	837
100		12.37	9.16	9.3	10.95	12.37	1065	1056	697	938	1065

Upper normal LH (8.6 IU/L) and lower normal testosterone (250 ng/dL) cutoffs were within ranges marked in bold print

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Erectile dysfunction in male survivors of childhood cancer

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Introduction

Male sexual dysfunction and its association with psychological and physical well-being have been underreported in childhood cancer survivors (CCSs). To our knowledge, this study provides the first data on a large population of systematically and clinically assessed CCSs, enumerating the prevalence and consequences of erectile dysfunction (ED) and identifying potential targets for intervention.

Methods

This cross-sectional, single-institution study included male CCSs, 18 years or older, 10 years or more from diagnosis of childhood cancer who completed questionnaires on sexual health.[1] In sexually active participants, mild to severe ED was defined by scores of 25 or less, using the validated, 6-item version of the International Index of Erectile Function.[2] In non–sexually active participants, responses to items that queried problems achieving or sustaining an erection were used to characterize ED. Low total testosterone level was defined as morning serum concentrations less than 250 ng/dL (to convert to nanomoles per liter, multiply by 0.0347). Psychological distress, body image dissatisfaction, and health-related quality of life were measured using the Brief Symptom Inventory, the Body Image Scale, and the 36-Item Short-Form Health Survey, respectively. Physical health outcomes included lean muscle mass, vitality, physical activity, slowness, weakness, and exercise tolerance.[3] This study was approved by the institutional review board at St Jude Children's Research Hospital; written informed consent was obtained from all participants.

To limit false-positive results, elastic net regression was used to select variables for multivariable analyses. Associations between demographic and treatment-related risk factors, psychological distress, physical health, and ED were evaluated (relative risk [RR], 95% CI). Statistical significance was set at $\alpha = .05$ (2-sided).

Results

The survey participant rate was 62.6% (1021 of 1631 eligible patients). A total of 1021 participants (median age, 31.3 years; range, 18.8-61.5 years) were included. ED scores were available for 956. Erectile dysfunction was reported by 277 (29.0%; 95% CI, 26.1%-32.0%) of the participants. In sexually active participants (n = 873 [85.5%]), independent risk factors for ED included Hispanic or other race/ethnicity (RR, 1.94; 95% CI, 1.05-3.61), age at the time of the study (RR, 0.98; 95% CI, 0.96-1.00), and low testosterone levels (RR, 1.70; 95% CI, 1.20-2.41) (Table). When data of both sexually and non–sexually active participants were combined, black race (RR, 1.51; 95% CI, 1.14-2.02) was also a risk factor for ED. Individuals with greater body image dissatisfaction and low lean muscle mass were more likely to report ED in both the sexually active and combined groups (Table).

Table. Multivariable analysis of factors and markers associated with ED among study participants

Characteristic	Sexually active participants (n=873)[a] Model 1. (n=238)[c]				All participants (n=1021)[b] Model 2. (n=277)[d]			
	No.	No. (Row %)	RR (95% CI)	*P* value	No.	No. (Row %)	RR (95% CI)	*P* value
Demographic-related factors								
Race/ethnicity								
Non-Hispanic white	725	198 (27.3)	1 [Ref]		837	229 (27.4)	1 [Ref]	
Non-Hispanic black	77	29 (37.7)	1.46 (0.98-2.17)	0.06	92	35 (38.0)	1.51 (1.14-2.02)	0.005
Hispanic/other	22	11 (50.0)	1.94 (1.05-3.61)	0.04	27	13 (48.2)	1.78 (1.19-2.66)	0.005
Age at diagnosis, mean (SD), y								
Mean (SD)	873	8.6 (5.6)	0.99 (0.97-1.02)	0.56	1021	8.4 (5.5)	NS	
Age at questionnaire, mean (SD), y								
Mean (SD)	873	32.7 (8.2)	0.98 (0.96-1.00)	0.05	1021	32.1 (8.4)	0.98 (0.97-1.00)	0.03
Treatment-related factors								
Illicit drug use								
No	688	206 (29.9)	1 [Ref]		802	240 (29.9)	1 [Ref]	
Yes	125	30 (24.0)	0.80 (0.54-1.18)	0.26	138	33 (23.9)	0.80 (0.59-1.08)	0.15
Testicular radiation								
None	786	223 (28.4)	NS		911	257 (28.2)	1 [Ref]	
Yes	38	15 (39.5)	NS		45	20 (44.4)	1.23 (0.87-1.74)	0.25
Cranial radiation dose								
None	588	154 (26.2)	1 [Ref]		678	182 (26.8)	1 [Ref]	
1-29 Gy	180	59 (32.8)	1.27 (0.91-1.78)	0.16	201	66 (32.8)	1.25 (0.98-1.60)	0.07
≥ 30 Gy	56	25 (44.6)	1.48 (0.93-2.37)	0.10	77	29 (37.7)	1.27 (0.91-1.78)	0.17
Surgery affecting ED								
No	761	214 (28.1)	1 [Ref]		884	252 (28.5)	1 [Ref]	
Yes	63	24 (38.1)	1.30 (0.84-2.00)	0.24	72	25 (34.7)	1.17 (0.85-1.61)	0.34
Low testosterone level								
No	626	157 (25.1)	1 [Ref]		716	181 (25.3)	1 [Ref]	
Yes	198	81 (40.9)	1.70 (1.20-2.41)	0.003	240	96 (40.0)	1.53 (1.18-1.99)	0.001

Table. (continued)

Characteristic	Sexually active participants (n=873)[a] Model 1. (n=238)[c] No.	No. (Row %)	RR (95% CI)	*P* value	All participants (n=1021)[b] Model 2. (n=277)[d] No.	No. (Row %)	RR (95% CI)	*P* value
Markers of physical condition								
Hand grip strength (weakness)								
No	788	225 (28.6)	1 [Ref]		912	260 (28.5)	1 [Ref]	
Yes	31	13 (41.9)	1.28 (0.71-2.28)	0.41	37	16 (43.2)	1.26 (0.73-2.15)	0.41
Poor physical activity								
No	525	136 (25.9)	1 [Ref]		607	156 (25.7)	1 [Ref]	
Yes	291	100 (34.4)	1.16 (0.88-1.54)	0.30	337	118 (35.0)	1.20 (0.92-1.56)	0.18
Low lean muscle mass								
No	645	174 (27.0)	1 [Ref]		745	201 (27.0)	1 [Ref]	
Yes	128	48 (37.5)	1.44 (1.04-2.00)	0.03	147	53 (36.1)	1.36 (1.00-1.86)	0.05
Markers of psychological distress								
Depression								
No	683	175 (25.6)	1 [Ref]		792	202 (25.5)	1 [Ref]	
Yes	125	56 (44.8)	1.41 (0.94-2.12)	0.09	144	67 (46.5)	1.42 (0.98-2.07)	0.07
Anxiety								
No	721	194 (26.9)	1 [Ref]		833	226 (27.1)	1 [Ref]	
Yes	87	37 (42.5)	1.22 (0.78-1.90)	0.38	103	43 (41.8)	1.09 (0.72-1.64)	0.69
Body image dissatisfaction, mean (SD)								
ED	235	1.6 (0.6)	1.28 (1.03-1.60)	0.02	274	1.6 (0.7)	1.32 (1.08-1.63)	0.01
No ED	581	1.4 (0.5)	1 [Ref]		674	1.4 (0.5)	1 [Ref]	

[a] Reported sexual activity during the 4 weeks prior to study participation.
[b] Reported sexual activity or no sexual activity during the 4 weeks prior to study participation.
[c] Analysis with International Index of Erectile Function (IIEF) scale (scores ≤25 are consistent with mild to severe ED).
[d] Analysis with IIEF scale or questionnaire response consistent with ED.
Abbreviations: ED, erectile dysfunction; NS, not selected for the model by the elastic net regression method; RR, relative risk

Discussion

The prevalence of ED in our study was considerably higher compared with other CCS cohorts or the general population.[4,5] Hypogonadism, a condition often undiagnosed in CCSs, could explain

the associations between low testosterone levels, low lean muscle mass, and ED.[6] We also found an association between nonwhite race/ethnicity and ED. The reasons for this association are not clear and need further exploration in populations enriched for racial/ethnic minorities. The finding that younger age at assessment was associated with a higher risk for ED is likely a reflection of the differential age distributions between tumor types in our population: protocols to treat patients with brain tumors were introduced at our institution in the mid-1980s. Therefore, this association is likely driven by including younger survivors treated for brain tumors, which is a population at risk for hypogonadism.[6]

The association between ED and greater body image dissatisfaction may be bidirectional and emphasizes that ED requires multidisciplinary treatment that combines psychological counseling and medical treatment. The lack of validated questionnaires has limited the reliable assessment of ED in non–sexually active CCSs; further diagnostic research is warranted. Furthermore, potential selection bias and misclassification may have overestimated the prevalence of ED in our cohort. Although the results from these analyses are hypothesis generating and need validation in an independent cohort, our data support the hypothesis that ED may be a modifiable condition in CCSs. Clinicians should be aware that appropriate management of hypogonadism may improve impaired sexual functioning in CCSs.

References

1. Hudson MM, Ness KK, Nolan VG, et al. Prospective medical assessment of adults surviving childhood cancer: study design, cohort characteristics, and feasibility of the St. Jude Lifetime Cohort study. *Pediatr Blood Cancer.* 2011;56(5):825-836.
2. Cappelleri JC, Rosen RC, Smith MD, Mishra A, Osterloh IH. Diagnostic evaluation of the erectile function domain of the International Index of Erectile Function. *Urology.* 1999;54(2):346-351.
3. Fried LP, Tangen CM, Walston J, et al; Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci.* 2001;56(3):M146-M156. .
4. Ritenour CW, Seidel KD, Leisenring W, et al. Erectile Dysfunction in Male Survivors of Childhood Cancer-A Report From the Childhood Cancer Survivor Study. *J Sex Med.* 2016;13(6):945-954.
5. Selvin E, Burnett AL, Platz EA. Prevalence and risk factors for erectile dysfunction in the US. *Am J Med.* 2007;120(2):151-157.
6. Chemaitilly W, Li Z, Huang S, et al. Anterior hypopituitarism in adult survivors of childhood cancers treated with cranial radiotherapy: a report from the St Jude Lifetime Cohort study. *J Clin Oncol.* 2015;33(5):492-500.

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Summary, general discussion and future perspectives

Summary, general discussion and future perspectives

The improvement in survival rates of children diagnosed with neoplasms mandates a better characterization of the development of adverse endocrine sequelae. In this thesis, we aimed to assess risk factors of hypothalamic obesity following craniopharyngioma or other suprasellar tumors, and to propose possibilities for new intervention strategies. In addition, we determined the prevalence, latency time, risk factors and associated clinical consequences of endocrine disorders following childhood cancer. Finally, we developed recommendations for surveillance of hypothalamic-pituitary dysfunction in survivors of childhood cancer.

Part I Individualized management of craniopharyngioma or other suprasellar tumors

Grading and risk factors of hypothalamic damage

Hypothalamic obesity is an endocrine sequela observed in up to 55% of patients following craniopharyngioma, that severely impacts quality of life with excess morbidity and mortality.[1] The degree of tumor involvement at diagnosis is predictive for the occurrence of hypothalamic obesity during follow-up care.[2,3] Several grading systems have been developed to assess pre- and post-operative hypothalamic involvement of craniopharyngioma.[4] These grading systems are the basis for surgical treatment algorithms, and have been reported to decrease the risk for severe post-operative weight gain.[5] In our study, we included 35 children and adults with craniopharyngioma and pre- and post-operative MRIs were retrospectively graded for hypothalamic involvement by two neuroradiologists (*Chapter 2*). Surprisingly, the interobserver agreement between the radiologists was low. A recent study by Muller et al. showed high concordance between surgical and neuroradiological assessment of pre-operative hypothalamic involvement. However, with respect to degree of resection and post-operative hypothalamic damage, surgeons reported to have performed more complete resections and lower rate of hypothalamic damage, when compared to reports from the neuroradiologists.[6] Neuroradiological assessment of post-operative hypothalamic damage had a higher predictive value for adverse hypothalamic sequelae (i.e. BMI) in this study. Other than differences in grading, we observed the development of hypothalamic obesity in 19 of 35 patients, of whom 8 patients experienced morbid obesity. Significant positive associations were observed between gross total resection (vs. partial resection) and hypothalamic obesity, as well as between hypothalamic obesity at diagnosis (vs. no hypothalamic obesity) and morbid obesity at last follow-up. In addition, we observed reduced event-free survival in patients after a partial resection (vs. gross total resection), which seemed to be overcome with adjuvant radiation therapy (RT). Our study emphasizes the importance of adequate and uniform assessments of pre- and post-operative hypothalamic damage, as these may be used to determine treatment strategies and to estimate risk profiles

for the development of hypothalamic obesity during follow-up care. Individualized treatment for craniopharyngioma should consider the risk for endocrine sequelae, such as hypothalamic obesity, in addition to the risk for tumor progression or recurrence.

Systematic review & individualized treatment algorithm for hypothalamic obesity

Hypothalamic obesity is a challenging condition; affected individuals do not seem to respond to standard management as well as individuals with non-tumor related ("community-type") obesity. Several reviews have summarized intervention studies for hypothalamic obesity, and results are generally negative.[7,8] However, as this form of obesity is multifactorial, an individualized treatment approach might be more helpful. When we identified intervention studies performed for hypothalamic obesity in patients with craniopharyngioma or other suprasellar tumors, many interventions were unsuccessful (*Chapter 3*). However, certain individuals benefited from specific interventions. Together with pathophysiological knowledge about hypothalamic obesity and the findings from the intervention studies, we developed an individualized treatment algorithm for hypothalamic obesity. This included six domains that serve as targets for anti-obesity treatment: psychosocial disorders, hyperphagia, sleep disturbances, energy expenditure, hyperinsulinemia and hypopituitarism. Individualized treatment strategies using these six domains, might be helpful to induce weight loss, although development of new (pharmacotherapeutic) agents is required.

Individualized dietary intervention for hypothalamic obesity

In obese children from the general population, comprehensive lifestyle modifications, including dietary modification, are the starting point for anti-obesity treatment.[9] In patients with hypothalamic obesity following craniopharyngioma or other suprasellar tumors, the effectiveness of dietary interventions is often questioned, although prospective studies are lacking (*Chapter 3*). In our one-year pilot intervention trial, we assessed the feasibility and effectiveness of an individualized dietary intervention, including an extensive coaching trajectory, in six children with acquired hypothalamic obesity (*Chapter 4*). Although temporary weight loss was observed, after completion of the intervention at one-year, overall BMI was similar compared to baseline. Despite lack of efficacy in terms of BMI reduction, participants and their parents were satisfied with the intervention and would recommend it to others. In addition, we identified several items that could improve dietary adherence: to encourage active parental involvement, to extend the coaching trajectory and to improve the user-friendliness of applications to self-report dietary intake. As dietary interventions will likely remain a first step in prevention or treatment of hypothalamic obesity, new strategies that achieve long-term, and eventually lifelong compliance to dietary restrictions are required.

Conclusions and future perspectives

In conclusion, the extent of pre- and postoperative hypothalamic damage by current imaging techniques is difficult to determine, as judgment differs among health care providers. This emphasizes the need for improvement of grading strategies to define hypothalamic damage, potentially by new MRI techniques. Treatment strategies that balance the extent of resection, timing of RT, risk for recurrence, and risk for hypothalamic sequelae are required. Centralizing the care for patients with craniopharyngioma, allows multidisciplinary and experienced teams to combine these factors and treat patients according to best available knowledge. As tumor- or treatment related hypothalamic damage can not always be prevented, initiation of interventions is required to prevent or treat hypothalamic obesity in a timely manner. This should start with extensive and repetitive dietary counseling, together with intensive coaching. A dietary intervention should extend beyond the outpatient endocrine clinic, in order to involve the patients' home environment. Additional interventions for hypothalamic obesity may be started in one or more of the six abovementioned clinical domains, to achieve optimal results.

Individualized treatment for craniopharyngioma, as well as for craniopharyngioma-related hypothalamic obesity may be a step towards improved overall health and quality of life in these patients. Regarding tumor treatment, improvement in neurosurgical or RT techniques, such as proton therapy, have the potential to limit damage to healthy surrounding tissues. In addition, novel agents, including targeted therapies with inhibitors (MEK/BRAF), are currently studied for specific subtypes of craniopharyngioma. The extent of treatment-related hypothalamic damage may be limited or prevented by using these targeted approaches. Furthermore, improvement in MRI techniques may better predict if hypothalamic damage has occurred before or following treatment, and facilitates multidisciplinary assessments to determine which specific hypothalamic nuclei are damaged. This may help define adequate pre-operative treatment strategies, and post-operative risk-based management for occurrence of hypothalamic obesity.

Although hypothalamic damage may be prevented by improvement in treatment strategies, late recognition and referral of patients may still result in significant hypothalamic damage at diagnosis of craniopharyngioma. Therefore, treatment strategies for hypothalamic obesity will continue to be necessary. Importantly, these interventions should be individualized to target affected clinical domains (i.e. psychosocial disorders, hyperphagia, sleep disturbances, energy expenditure, hyperinsulinemia and hypopituitarism), and involve multidisciplinary collaborations. A prospective interventional study is ideally required to fully evaluate our proposed treatment algorithm. An extended protocol would be necessary to report overall effectiveness; but this will be challenging in a cohort of patients receiving a variety of individualized interventions. Multi-center collaborations are more likely to improve generalizability of the results and achieve larger sample sizes.

Future directions

- To optimize treatment strategies for craniopharyngioma that limit the extent of hypothalamic damage, but minimize the risk of tumor recurrence or progression.
- To assess if individualized treatment for hypothalamic obesity, including targeting different domains simultaneously, is effective for weight reduction.

Part II Screening for endocrine disorders after childhood cancer

Hypothalamic-pituitary disorders

High prevalence of hypothalamic-pituitary disorders in children with cancer

Children diagnosed and treated for cancer are at increased risk for developing growth hormone deficiency (GHD), luteinizing hormone/follicle-stimulating hormone deficiency (LH/FSHD), thyroid-stimulating hormone deficiency (TSHD), adrenocorticotropic hormone deficiency (ACTHD) and central precocious puberty (CPP). Abnormalities in hypothalamic-pituitary (HP) functioning are generally observed in children who have tumors in the HP region, or following high-dose cranial RT, with an estimated overall prevalence up to 54.8%.[10,11,12] Although the overall prevalence of HP disorders is high, the prevalence of each distinct HP disorder varies. In our cohort study, we included 355 children and adolescents at high risk for HP disorders; all children were exposed to high-dose RT (50.4-59.4 Gy) and 29% had tumor involvement of the HP region. After more than 10 years of systematic and frequent endocrine evaluations, we observed a high prevalence of all HP disorders, comparable to previous cohorts (37.2% for GHD, 17.7% for LH/FSHD, 14.9% for TSHD, 10.3% for ACTHD and 12.6% for CPP) (*Chapter 5*).[10,12-14] The prevalence of HP disorders was highest among patients with tumor involvement in the HP region, including 56.3% with GHD and 39.7% with CPP.

In childhood cancer survivors without previous cranial RT exposure or HP tumor involvement, the prevalence of HP disorders is considered negligible and ongoing screening is generally not recommended.[15] In the St. Jude Lifetime Cohort (SJLIFE) study, long-term childhood cancer survivors receive regular health screenings including core laboratory tests, physical performance assessments, and questionnaires regarding psychosocial health (*Chapter 6*).[16] This study, initiated in 2007, enables longitudinal clinical and endocrine evaluation in all survivors, regardless of previous treatment exposures. Our SJLIFE report on HP disorders included 3141 adult survivors of childhood cancer (median follow-up 24.1 years after diagnosis) and the prevalence of HP disorders in survivors without cranial RT exposure or HP tumor involvement could be assessed. These results showed that the estimated prevalence was 6.2% for GHD, but <1% for other HP

disorders (*Chapter 6*). In these cases of GHD, other potential mechanisms may have resulted in HP damage, such as leukemic infiltration, hydrocephalus or another CNS insult.[17,18]

Early- and late-onset of HP disorders

Knowledge about the specific onset of HP disorders in survivorship determines when and how often surveillance for HP disorders should be performed. In addition, latency times help to determine the need for lifelong surveillance. Current findings for latency times are mainly derived from studies with prospective but short follow-up periods [18,19], or from retrospective cohort-studies (*Chapter 9*).[13,20] In general, the latency time of HP disorders following direct tumor- or treatment- (i.e. surgery) related HP injury is considered short, while radiation-induced HP disorders generally unfold over a longer period of time.[21-23] Children included in our study received frequent and longitudinal endocrine assessments, which allowed for a determination of the specific onset of HP disorders (*Chapter 5*). We observed that a high proportion of HP disorders was present prior to the initiation of cranial RT; this included ~20% for GHD, TSHD and ACTHD, >50% for CPP and <5% for LH/FSHD, potentially as consequences of HP tumor involvement. Following cranial RT, median latency times ranged between 1.6 and 3.2 years for GHD, TSHD, ACTHD and CPP, and 7 years for LH/FSHD. Patients with tumor involvement in the HP region demonstrated shorter latency times when compared to patients without HP tumor involvement. In addition, HP disorders developed as early as 0.5 years following RT, but they could develop up to 17 years after treatment. These results suggest a general trend of early occurrence of HP disorders after RT, but also that at-risk individuals require endocrine screening for an extended period of time after completion of therapy.

Extending knowledge about risk factors for HP disorders

Knowledge about demographic- and treatment-related risk factors of HP disorders will assist in determining which survivors require endocrine screening. As mentioned above, a well-known risk factor for the development of HP disorders in survivors is exposure to cranial RT. The occurrence of HP disorders is typically dose-dependent, with a higher RT dose resulting in a higher risk for HP disorders.[10,21] For example, a high prevalence of TSHD, LH/FSHD and ACTHD has been reported after higher doses of cranial RT (i.e. >30 Gy); however, GHD and CPP have been observed after doses ranging between 18 and 30 Gy.[24-26] Therefore, certain guidelines currently recommend screening for TSHD, LH/FSHD and ACTHD only for survivors exposed to high-dose cranial RT.[15,27] However, establishing dose-response relationships between RT and occurrence of HP disorders requires cohorts that include patients exposed to high, moderate and low dose RT, as well as patients without previous RT exposure (i.e. comparison populations). In addition, specific dosimetry data defining the RT dose response to the hypothalamus and pituitary gland provides more accurate data about the vulnerability of the HP region, when compared to estimations from overall cranial RT doses. In our SJLIFE report, 1086 participants

(34.6%) were exposed to different RT doses and 2055 (65.4%) were not exposed to cranial RT (*Chapter 6*). In addition, specific HP dosimetry data were available for a majority of the cohort (84.8%). We demonstrated significant positive associations between GHD, TSHD and LH/FSHD with relatively lower (< 30 Gy) cranial RT doses, when compared to no cranial RT. In contrast, higher cranial RT doses (i.e. > 30 Gy) were associated with a higher risk for ACTHD; however, no comparison group (i.e. no survivors without cranial RT) was available for this HP axis. These results suggest that specific dose cut-offs to determine survivors at-risk for HP disorders are difficult to implement; survivors appear to be at-risk for TSHD and LH/FSHD at relatively low doses of cranial RT, albeit to a lesser extent when compared to GHD. Our results justify the recently updated surveillance recommendations from the Children's Oncology Group, where specific dose-cut offs have been removed to define at-risk populations, except for ACTHD.[28]

The contribution of chemotherapy to the risk of HP injury remains controversial.[29] HP dysfunction following chemotherapy, in the presence or absence of exposure to cranial RT, has only been reported in small case series; therefore, the exact pathophysiological mechanism remains unclear. In our SJLIFE report, we observed positive associations between alkylating agents with an increased risk for GHD and LH/FSHD (*Chapter 6*). Furthermore, a positive association between intrathecally-administered chemotherapy and GHD was reported. Secondly, in the general pediatric population, acquired HP disorders are observed after traumatic brain injury with a prevalence ranging between 5% and 57%.[30,31] In survivors of childhood cancer, there were insofar no specific data regarding the additional risk brought about by brain injury (e.g. increased intracranial pressure, cerebral thrombosis or cerebral hemorrhage) (*Chapter 9*). In the SJLIFE cohort, we demonstrated positive associations between all HP disorders with central nervous system (CNS) injury, including stroke, epilepsy and hydrocephalus (*Chapter 6*). Limitations of this study include: the use of non-standard screening tests for several HP disorders (e.g. insulin-like growth factor 1 (IGF-1) for GHD), mutual etiological risk factors for HP disorders and brain injury (i.e. CNS tumor, cranial RT exposure) and exact onset of HP disorders in relation to CNS injury could not be determined.

Recommendations for surveillance of HP disorders

In *Chapter 9*, we report the recommendations for HP dysfunction surveillance for childhood, adolescent and young adult cancer survivors from the International Guideline Harmonization Group (IGHG). For this process, all existing surveillance guidelines for HP dysfunction were collected, and we identified concordances and discordances among these guidelines. A panel of 42 experts formulated clinical questions for items that were discordant across guidelines. These covered four main issues: 1) Who needs surveillance?; 2) When should surveillance be initiated? At what frequency and for how long should surveillance be performed; 3) What surveillance modality should be used?; 4) What should be done when abnormalities are identified? Through

a systematic literature search, we identified, summarized and graded the available literature that covered these four topics. We then formulated recommendations based on the available evidence and expert opinion. The completion of final recommendations will allow for optimal and uniform surveillance for HP disorders among all childhood cancer survivors. In addition, the guideline harmonization effort has exposed the paucity of high-quality evidence in certain areas and identified gaps in knowledge, which may serve as topics for future research.

Male hypergonadotropic hypogonadism

Reproductive outcomes including male infertility are the focus of many reports on survivors who received gonadotoxic therapy, but literature about impaired testosterone production due to Leydig cell failure (LCF) is scarce.[32] Current known risk factors for LCF include testicular RT, and to a lesser extent, exposure to alkylating agents.[32] However, LCF is often defined as subclinical or compensated failure in the existing literature, which include elevated LH levels but normal testosterone levels.[33] In our SJLIFE report, we observed a prevalence of LCF (i.e. testosterone below the reference ranges, with elevated LH levels) of 8.0% as well as 22.8% for compensated LCF (i.e. elevated LH levels, but normal testosterone levels). These ranges were comparable to other cohort studies (C*hapter 10*).[34] Risk factor associations were similar for both LCF and compensated LCF, which included higher age at follow-up, testicular RT and exposure to alkylating agents. In the literature, an increased risk for LCF has been reported after exposure to relatively large RT doses (i.e. ≥20 Gy), but this has only been shown in short term follow-up studies.[35] Our study that included long-term follow-up up to 22 years, revealed an increased risk for LCF; importantly, this was shown with smaller doses (i.e. <20 Gy). In addition, we observed a higher risk for LCF after increased doses of alkylating agents.

Conclusions and future directions

In conclusion, our findings support an increased risk for all HP disorders after high-dose cranial RT. Survivors exposed to low- dose cranial RT appear to be at-risk for HP dysfunction, including GHD, and to a lesser extent TSHD and LH/FSHD. Furthermore, survivors of childhood cancer are at increased risk for HP disorders related to primary cancer location in the HP region, but also specific treatment modalities that extend beyond cranial RT, and tumor- or treatment-related complications associated with CNS injury. A high proportion of HP disorders is already observed prior to the initiation of RT, which demonstrates the need for endocrine screening prior to RT in all patients with CNS tumors involving the HP region. Despite the general trend of early occurrence of HP disorders after RT, patients require extended endocrine screening given the continued occurrence of new diagnoses several years after the completion of therapy. Furthermore, we developed surveillance recommendations that incorporate current knowledge about who, when and how to screen for HP disorders, but we also identified gaps in the literature. Finally, we

emphasize that LCF and compensated LCF are not uncommon in survivors, and we identified risk factor associations that can be used to determine which survivors require close monitoring for LCF.

The results of these studies aim to increase knowledge about the prevalence, risk factors and latency times of endocrine disorders following childhood cancer. Incorporation of this knowledge into surveillance guidelines will assist in accurately detecting and referring survivors to a specialist (endocrinology provider for children or adults as appropriate) in a timely manner. Future steps include the completion, implementation and monitoring of the HP dysfunction surveillance guideline, and to evaluate our strategies for cost-effectiveness. Feasibility of the guideline, the time to referral, true and false positive screening results, and burden of screening on patients should be evaluated. Additionally, the current IGHG surveillance guideline for gonadotoxicity in males can be updated with knowledge from our SJLIFE report on LCF and compensated LCF.[32]

Secondly, the gaps in research that we identified should be addressed in future studies. Validation of our results is needed with other cohorts, such as risk factor-associations with lower doses of RT, CNS injury and chemotherapy. The pathophysiology of chemotherapy-induced HP injury and injury associated with CNS insults such as stroke, epilepsy and hydrocephalus, should be elucidated. Additional studies that include dosimetry data for the HP region are required to accurately assess dose-response relationships between RT and HP disorders. There is need to assess (immune-mediated) HP disorders that may occur after newer treatment modalities, including targeted therapies, immunotherapies and proton RT, ideally by setting up systematic and longitudinal endocrine evaluations in large, possibly multicenter cohorts.

Finally, data about HP disorders in childhood cancer survivors mainly derive from population-based studies. Exact pathophysiological mechanisms for HP injury remain unclear, and potential targets for prevention of HP damage that extend beyond improving cancer treatment strategies themselves, are unknown. Collaborations between clinical and basic researchers may extend this knowledge by investigating how treatment modalities induce HP injury, and more specifically, why some HP axes seem more sensitive to treatment compared to others. Another direction may involve investigating the effect of genetic factors similarly to a recent work on premature menopause in the SJLIFE cohort.[36] This type of information may inform with better precision HP disorder risk, allowing more accurate risk prediction and potentially identifying targets for early intervention. Besides determining high susceptibility for endocrine late effects, these associations may also provide insights into the specific pathways involved in HP damage.

Future directions

- To implement and evaluate surveillance recommendations for HP disorders.
- To assess the risk and dose-response relationships for HP disorders after established treatment strategies and CNS injury, but also after newer treatment modalities.
- To establish large cohorts of children of cancer who received longitudinal and systematic endocrine screening from diagnosis onwards.
- To assess pathophysiological mechanisms involved in development of HP disorders.
- To identify genetic factors that contribute to development of HP disorders.

Part III Screening modalities and treatment of endocrine disorders after childhood cancer

Limited knowledge pertaining to optimal screening strategies for HP disorders

The number of individuals surviving a childhood cancer is on the rise with a growing proportion making it to long-term follow-up.[37] This emphasizes the need to optimize screening modalities in a growing number of at-risk yet, asymptomatic survivors. This optimization should aim at reducing false-positive and false-negative findings in order to minimize the burden and cost of unnecessary procedures without depriving individuals from the benefits of a timely diagnosis and early interventions. However, studies that have assessed the optimal screening modalities for HP disorders in survivors of childhood cancer are limited (*Chapter 9*). Although we can apply screening modalities from the general population, there are characteristics particular to survivors that may require adjustments. For example, there may be difficulties with the interpretation of physical examination, such as measuring testicular volumes to assess pubertal development, which may not be reliable after gonadotoxic therapy in boys. Also, growth disturbances may be the consequence of HP disorders, but also of craniospinal RT or other tumor- or treatment-related effects on the skeleton. Seemingly normal growth velocity may be seen if CPP and GHD occur simultaneously. Furthermore, there may be difficulties in the interpretation of laboratory results, as central and primary organ damage may overlap.

Only three studies in children have demonstrated a moderate diagnostic value of IGF-1 and IGFBP-3 for the diagnosis of GHD, in line with a recent systematic review (*Chapter 9*).[38-41] We did not identify any studies that included the best screening modality for LH/FSHD and CPP, specifically in survivors. Regarding screening for ACTHD, in one study poor agreement was observed between morning cortisol and low-dose ACTH testing to detect ACTHD in children.[42] These results imply that, until new diagnostic studies are available in childhood cancer survivors, for GHD, ACTHD, LH/FSHD and CPP, clinicians are left to rely on existing screening guidelines

from the general population. However, health care providers should be aware of the caveats in screening for HP disorders in survivorship.

The diagnosis TSHD is challenging, as it mainly relies on measuring plasma free thyroxine (FT4) concentrations. TSHD is often defined by a FT4 concentration below the reference range, in combination with low, normal or mildly elevated TSH levels. However, the use of strict population-based FT4 cut-off values to differentiate between hypothyroid and euthyroid states in survivors, but also in the general population, are questionable. Individual FT4 concentrations are kept within a narrow range (setpoint)[43], while variability of FT4 concentrations between individuals is large.[44] Dynamic testing with thyrotropin-releasing hormone or rise in nocturnal TSH have been suggested as alternative markers of TSHD in survivors of childhood cancer [45]; however, another study demonstrated no correlation between FT4 concentrations with dynamic testing or nocturnal TSH rise (*Chapter 9*).[46] A different approach is to assess the individual reductions in FT4 concentrations, which may indicate development of TSHD over time. In survivors of childhood cancer exposed to cranial RT, a population at-risk for TSHD, FT4 levels are often longitudinally measured. This allows observation of individual trends in FT4 concentrations over time. In our retrospective cohort that included 207 survivors of childhood brain tumors, we demonstrated a decline in longitudinally measured FT4 concentrations (i.e. 21%) over time after exposure to cranial RT (*Chapter 7*). Furthermore, the decline in FT4 concentrations exceeded 40% in patients from the time of RT exposure to diagnosis of TSHD. In patients without the diagnosis of TSHD, a FT4 decline was observed, although to a smaller extent (i.e. 12%). Limitations of this study included non-systematic screening of FT4 concentrations resulting in missing data, and the co-existence of primary thyroid damage due to craniospinal RT. Therefore, we validated our results in a cohort of 267 children exposed to cranial RT who received systematic screening with FT4 after RT treatment (*Chapter 8*). Using longitudinal analysis, we demonstrated a decline in FT4 following RT; we also demonstrated associations between female gender and younger age at RT with greater FT4 declines.

Clinical consequences of endocrine disorders

HP disorders - physical and neurocognitive outcomes

Clinical consequences of HP disorders in childhood cancer survivors may be similar to those observed in the general population. However, studies that are specific to cancer survivors are limited and primarily address adverse effects after GHD, including short stature, impaired bone health and adverse metabolic profiles.[10,47-51] Associations have been observed between LH/FSHD, bone mineral deficits (BMD) and adverse metabolic profiles, as well as between CPP and short stature in survivors.[10,49] In our relatively young cohort (17.8 years old at follow-up), we included 355 children exposed to high-dose RT. This cohort received systematic and frequent endocrine

screening, which allowed for the early detection and treatment of HP disorders, with potential prevention of endocrine-related adverse health effects (*Chapter 5*). We observed associations between the presence of GHD with low BMD and short stature, despite treatment with GH in 64% of patients. Concerns of GH safety may have delayed GH treatment or resulted in interruptions or complete cessation, which may have resulted in these adverse physical outcomes. Other than the association between TSHD and dyslipidemia, no other associations between adverse physical health and HP disorders were observed in our cohort. Adverse physical effects of HP disorders may have been prevented by early and systematic screening, including using proper hormone replacement therapies. In the SJLIFE report that included adult survivors (31.7 years old at follow-up), HP disorders were associated with many poor physical outcomes. This included: short stature (GHD and TSHD), severe BMD deficit (GHD, LH/FSHD), obesity (LH/FSHD), frailty (GHD), worse physical health-related quality of life (TSHD) and psychosexual dysfunction (LH/FSHD) (*Chapter 6*). The high prevalence of untreated HP disorders and late detection of HP disorders, may have contributed to these significant associations in this cross-sectional study. In both studies (C*hapters 5 and 6*), we also observed neurocognitive impairment associated with HP disorders, especially for the memory, attention and intelligence domains. Although associations between HP disorders and poorer neurocognitive functioning have been reported in the general population, our associations may be the consequence of mutual risk factors (i.e. cranial RT, CNS tumors), rather than causal relationships.[52,53] It may also reflect the extent of brain damage that is seen in children with CNS tumors.

HP disorders - GH safety

The safety of GH treatment in children who survived cancer remains controversial. Two recent meta-analyses demonstrated no increased risk for tumor recurrence and secondary neoplasms after GH treatment in childhood cancer survivors, although uncertainty in the evidence existed.[54] Our study confirms the safety of GH with respect to tumor recurrence, second neoplasms and mortality rates (*Chapter 5*).

Longitudinal FT4 trends and physical or neurocognitive outcomes

Emerging data demonstrate that subtle variations of thyroid function can have a negative impact on health outcomes, including cardiovascular, metabolic and bone health and neuropsychological functioning.[55] However, data mainly derives from cross-sectional study designs and predominantly variations in TSH concentrations are assessed. In our longitudinal study, we demonstrated associations between lower or declining FT4 concentrations with a decrease in height and increase in weight (*Chapter 8*). In addition, lower baseline but not declining FT4 concentrations were associated with higher risk for glucose disorder and dyslipidemia, but not for high fat mass. Neurocognitive functioning was only negatively influenced in the intelligence domain by declining FT4 concentrations.

Clinical consequences of hypogonadism

Sexual health, which depends on a range of physical, psychological and social factors, is recognized as a component of overall health and quality of life.[56,57] In childhood cancer survivors, sexual dysfunction is associated with poor quality of life and impaired general and mental health, such as depression and anxiety.[58,59] In the SJLIFE cohort, we demonstrated a prevalence of erectile dysfunction of 29.0% in males (*Chapter 11*), which is notably higher than the general population of men younger than age 40 (2-14%) or other childhood cancer survivor cohorts (12.3%).[60,61] Individuals with greater body image dissatisfaction were more likely to report erectile dysfunction, which may be a bidirectional association. The significant association between low testosterone or low lean muscle mass, both indicating hypogonadism, with erectile dysfunction in our study can be explained by the recognized role of androgens in normal male sexual functioning.[62] Low testosterone following cancer treatment may be the consequence of primary gonadal damage or central deficiencies of LH and FSH. Indeed, in our SJLIFE report, we found an association between LCF and erectile dysfunction, but not with compensated LCF (*Chapter 10*). Other associations with LCF included obesity, diabetes mellitus, mortality, frailty and depression, predominantly in survivors not receiving testosterone replacement. These associations cannot infer causality; burden from chronic disease may also result in low testosterone levels and the results may reflect the decision for non-treatment of participants with significantly impaired physical functioning. In our SJLIFE report on HP disorders, presence of LH/FSHD was significantly associated with impaired psychosexual function in survivors (*Chapter 6*). When this analysis was separated by gender, both females and males with LH/FSHD tended to report more often psychosexual dysfunction, although the association was only significant for females. Overall, the challenges in current follow-up care include the identification and treatment of hypogonadism, psychosexual dysfunction in both male and female survivors, as well as the psychological and physical effects of hypogonadism and psychosexual dysfunction.

Conclusions and future perspectives

In conclusion, our findings demonstrate that there are limited data to guide optimal screening strategies for HP disorders in survivors of childhood cancer. Addressing knowledge gaps in this area may potentially reduce the burden and cost of unnecessary procedures. For instance, we showed that lower or declining FT4 concentrations were associated predominantly with physical, and to a lesser extent neurocognitive adverse outcomes. Improving knowledge on how to interpret FT4 trends and not solely rely on given laboratory cut-off values may allow the individualization of thyroid hormone replacement therapy in the future. Additionally, we observed associations between HP disorders and adverse physical and neurocognitive health outcomes likely as the consequence of untreated HP disorders. These results highlight the need for adequate detection and treatment of HP disorders which may continue to unfold throughout

adulthood and middle age. Finally, the presence of hypogonadism and its association with impaired physical and psychosexual dysfunction highlight the need to better understand the barriers to the diagnosis of hypogonadism, and improve the management of sex hormone deprivation in survivors. The high prevalence of sexual dysfunction emphasizes the need for multidisciplinary management strategies combining psychological counseling and medical treatment.

Gaps in research include limited knowledge pertaining to optimal screening strategies for HP disorders in childhood cancer survivors. Cross-sectional diagnostic studies for HP disorders, including a homogeneous patient cohort who receive index and reference standard testing, are needed for both children and adults. Ethical concerns do not allow assessing the benefit of hormone replacement therapy via randomized studies given the known beneficial effect of treatment in the general population, particularly for children. Therefore, a prospective intervention study with baseline and follow-up measurements after intervention in a homogeneous cohort in children and adults, may be an alternative. Large cohorts and relatively long follow-up durations may be required to demonstrate significant effects for cardiovascular, metabolic and bone health outcomes. Current literature on the safety of GH replacement is biased because GH replacement is generally initiated in patients with a good prognosis. Also, GH replacement is often started greater than one year after treatment completion, which makes it difficult to assess optimal timing for the initiation of GH. In addition, second neoplasms generally evolve after longer follow-up periods, and these may only be detected with long prospective studies. Matched case-control studies may therefore add value to knowledge of GH safety.

With our longitudinal study, we hypothesize that FT4 trends rather than a particular cut-off concentration may better distinguish hypothyroid from euthyroid state in individuals, given the association between such trends and adverse health outcomes. However, our results should be validated in other cohorts. Future intervention studies could assess the benefits of individualized replacement with thyroid hormone based on FT4 levels, FT4 trends and presence of co-morbid conditions (e.g. obesity, growth impairment, etc.). Finally, barriers to the diagnosis and management of hypogonadism as well as those pertaining to sexual health communication and the lasting benefits of early diagnosis and treatment of hypogonadal states should be explored in future research.

Future directions

- To assess and implement optimal screening modalities for HP disorders in survivors of childhood cancer
- To evaluate the benefits and harms of hormone replacement for endocrine disorders (including HP disorders and hypergonadotropic hypogonadism) with prospective intervention studies.
- To evaluate if survivors benefit from individualized treatment with thyroxine hormone based on FT4 levels, FT4 trends and presence of co-morbid conditions.

References

1. Karavitaki N, Brufani C, Warner JT, et al. Craniopharyngiomas in children and adults: systematic analysis of 121 cases with long-term follow-up. *Clin Endocrinol (Oxf).* 2005;62(4):397-409.
2. Muller HL, Gebhardt U, Teske C, et al. Post-operative hypothalamic lesions and obesity in childhood craniopharyngioma: results of the multinational prospective trial KRANIOPHARYNGEOM 2000 after 3-year follow-up. *Eur J Endocrinol.* 2011;165(1):17-24.
3. de Vile CJ, Grant DB, Hayward RD, Kendall BE, Neville BG, Stanhope R. Obesity in childhood craniopharyngioma: relation to post-operative hypothalamic damage shown by magnetic resonance imaging. *J Clin Endocrinol Metab.* 1996;81(7):2734-2737.
4. Muller HL. Preoperative staging in childhood craniopharyngioma: standardization as a first step towards improved outcome. *Endocrine.* 2016;51(1):1-3.
5. Elowe-Gruau E, Beltrand J, Brauner R, et al. Childhood craniopharyngioma: hypothalamus-sparing surgery decreases the risk of obesity. *J Clin Endocrinol Metab.* 2013;98(6):2376-2382.
6. Muller HL, Reichel J, Boekhoff S, et al. Low concordance between surgical and radiological assessment of degree of resection and treatment-related hypothalamic damage: results of KRANIOPHARYNGEOM 2007. *Pituitary.* 2018;21(4):371-378.
7. Shah E, Lodh R, Siddell P, Morrall MC. Interventions for managing weight change following paediatric acquired brain injury: a systematic review. *Dev Med Child Neurol.* 2016;58(10):1004-1008.
8. Wang KW, Chau R, Fleming A, et al. The effectiveness of interventions to treat hypothalamic obesity in survivors of childhood brain tumours: a systematic review. *Obes Rev.* 2017;18(8):899-914.
9. Styne DM, Arslanian SA, Connor EL, et al. Pediatric Obesity-Assessment, Treatment, and Prevention: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2017;102(3):709-757.
10. Chemaitilly W, Li Z, Huang S, et al. Anterior hypopituitarism in adult survivors of childhood cancers treated with cranial radiotherapy: a report from the St Jude Lifetime Cohort study. *J Clin Oncol.* 2015;33(5):492-500.
11. Armstrong GT, Liu Q, Yasui Y, et al. Long-term outcomes among adult survivors of childhood central nervous system malignancies in the Childhood Cancer Survivor Study. *J Natl Cancer Inst.* 2009;101(13):946-958.
12. Gan HW, Phipps K, Aquilina K, Gaze MN, Hayward R, Spoudeas HA. Neuroendocrine Morbidity After Pediatric Optic Gliomas: A Longitudinal Analysis of 166 Children Over 30 Years. *J Clin Endocrinol Metab.* 2015;100(10):3787-3799.
13. Clement SC, Schouten-van Meeteren AY, Boot AM, et al. Prevalence and Risk Factors of Early Endocrine Disorders in Childhood Brain Tumor Survivors: A Nationwide, Multicenter Study. *J Clin Oncol.* 2016;34(36):4362-4370.
14. Armstrong GT, Conklin HM, Huang S, et al. Survival and long-term health and cognitive outcomes after low-grade glioma. *Neuro Oncol.* 2011;13(2):223-234.
15. Sklar CA, Antal Z, Chemaitilly W, et al. Hypothalamic-Pituitary and Growth Disorders in Survivors of Childhood Cancer: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2018;103(8):2761-2784.
16. Hudson MM, Ness KK, Nolan VG, et al. Prospective medical assessment of adults surviving childhood cancer: study design, cohort characteristics, and feasibility of the St. Jude Lifetime Cohort study. *Pediatr Blood Cancer.* 2011;56(5):825-836.
17. Quigg TC, Haddad NG, Buchsbaum JC, Shih CS. Hypothalamic obesity syndrome: rare presentation of CNS+ B-cell lymphoblastic lymphoma. *Pediatr Blood Cancer.* 2012;59(5):930-933.

18. Merchant TE, Rose SR, Bosley C, Wu S, Xiong X, Lustig RH. Growth hormone secretion after conformal radiation therapy in pediatric patients with localized brain tumors. *J Clin Oncol.* 2011;29(36):4776-4780.
19. Laughton SJ, Merchant TE, Sklar CA, et al. Endocrine outcomes for children with embryonal brain tumors after risk-adapted craniospinal and conformal primary-site irradiation and high-dose chemotherapy with stem-cell rescue on the SJMB-96 trial. *J Clin Oncol.* 2008;26(7):1112-1118.
20. Shalitin S, Gal M, Goshen Y, Cohen I, Yaniv I, Phillip M. Endocrine outcome in long-term survivors of childhood brain tumors. *Horm Res Paediatr.* 2011;76(2):113-122.
21. Clayton PE, Shalet SM. Dose dependency of time of onset of radiation-induced growth hormone deficiency. *J Pediatr.* 1991;118(2):226-228.
22. Merchant TE, Conklin HM, Wu S, Lustig RH, Xiong X. Late effects of conformal radiation therapy for pediatric patients with low-grade glioma: prospective evaluation of cognitive, endocrine, and hearing deficits. *J Clin Oncol.* 2009;27(22):3691-3697.
23. Clement SC, Schoot RA, Slater O, et al. Endocrine disorders among long-term survivors of childhood head and neck rhabdomyosarcoma. *Eur J Cancer.* 2016;54:1-10.
24. Shalitin S, Phillip M, Stein J, Goshen Y, Carmi D, Yaniv I. Endocrine dysfunction and parameters of the metabolic syndrome after bone marrow transplantation during childhood and adolescence. *Bone Marrow Transplant.* 2006;37(12):1109-1117.
25. Brennan BM, Rahim A, Mackie EM, Eden OB, Shalet SM. Growth hormone status in adults treated for acute lymphoblastic leukaemia in childhood. *Clin Endocrinol (Oxf).* 1998;48(6):777-783.
26. Darzy KH, Shalet SM. Hypopituitarism following radiotherapy. *Pituitary.* 2009;12(1):40-50.
27. Deutsche Gesellschaft fur Kinderendocrinologie und –diabetologie and Pädiatrische Onkologie und Hämatologie
28. Children's Oncology Group: Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers. [Internet]. Version 5.0. 2018. Available from: http://www.survivorshipguidelines.org/. (accessed February 2, 2019).
29. Crowne E, Gleeson H, Benghiat H, Sanghera P, Toogood A. Effect of cancer treatment on hypothalamic-pituitary function. *Lancet Diabetes Endocrinol.* 2015;3(7):568-576.
30. Casano-Sancho P. Pituitary dysfunction after traumatic brain injury: are there definitive data in children? *Arch Dis Child.* 2017;102(6):572-577.
31. Ghigo E, Masel B, Aimaretti G, et al. Consensus guidelines on screening for hypopituitarism following traumatic brain injury. *Brain Inj.* 2005;19(9):711-724.
32. Skinner R, Mulder RL, Kremer LC, et al. Recommendations for gonadotoxicity surveillance in male childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup Consortium. *Lancet Oncol.* 2017;18(2):e75-e90.
33. Howell SJ, Radford JA, Ryder WD, Shalet SM. Testicular function after cytotoxic chemotherapy: evidence of Leydig cell insufficiency. *J Clin Oncol.* 1999;17(5):1493-1498.
34. Greenfield DM, Walters SJ, Coleman RE, et al. Prevalence and consequences of androgen deficiency in young male cancer survivors in a controlled cross-sectional study. *J Clin Endocrinol Metab.* 2007;92(9):3476-3482.
35. Sklar CA, Robison LL, Nesbit ME, et al. Effects of radiation on testicular function in long-term survivors of childhood acute lymphoblastic leukemia: a report from the Children Cancer Study Group. *J Clin Oncol.* 1990;8(12):1981-1987.
36. Brooke RJ, Im C, Wilson CL, et al. A High-risk Haplotype for Premature Menopause in Childhood Cancer Survivors Exposed to Gonadotoxic Therapy. *J Natl Cancer Inst.* 2018;110(8):895-904.

37. Robison LL, Hudson MM. Survivors of childhood and adolescent cancer: life-long risks and responsibilities. *Nat Rev Cancer.* 2014;14(1):61-70.

38. Sklar C, Sarafoglou K, Whittam E. Efficacy of insulin-like growth factor binding protein 3 in predicting the growth hormone response to provocative testing in children treated with cranial irradiation. *Acta Endocrinol (Copenh).* 1993;129(6):511-515.

39. Tillmann V, Shalet SM, Price DA, et al. Serum insulin-like growth factor-I, IGF binding protein-3 and IGFBP-3 protease activity after cranial irradiation. *Horm Res.* 1998;50(2):71-77.

40. Hua C, Wu S, Chemaitilly W, Lukose RC, Merchant TE. Predicting the probability of abnormal stimulated growth hormone response in children after radiotherapy for brain tumors. *Int J Radiat Oncol Biol Phys.* 2012;84(4):990-995.

41. Sfeir JG, Kittah NEN, Tamhane SU, et al. Diagnosis of GH Deficiency as a Late Effect of Radiotherapy in Survivors of Childhood Cancers. *J Clin Endocrinol Metab.* 2018;103(8):2785-2793.

42. Patterson BC, Truxillo L, Wasilewski-Masker K, Mertens AC, Meacham LR. Adrenal function testing in pediatric cancer survivors. *Pediatr Blood Cancer.* 2009;53(7):1302-1307.

43. Benhadi N, Fliers E, Visser TJ, Reitsma JB, Wiersinga WM. Pilot study on the assessment of the setpoint of the hypothalamus-pituitary-thyroid axis in healthy volunteers. *Eur J Endocrinol.* 2010;162(2):323-329.

44. Andersen S, Pedersen KM, Bruun NH, Laurberg P. Narrow individual variations in serum T(4) and T(3) in normal subjects: a clue to the understanding of subclinical thyroid disease. *J Clin Endocrinol Metab.* 2002;87(3):1068-1072.

45. Rose SR, Lustig RH, Pitukcheewanont P, et al. Diagnosis of hidden central hypothyroidism in survivors of childhood cancer. *J Clin Endocrinol Metab.* 1999;84(12):4472-4479.

46. Darzy KH, Shalet SM. Circadian and stimulated thyrotropin secretion in cranially irradiated adult cancer survivors. *J Clin Endocrinol Metab.* 2005;90(12):6490-6497.

47. Link K, Moell C, Garwicz S, et al. Growth hormone deficiency predicts cardiovascular risk in young adults treated for acute lymphoblastic leukemia in childhood. *J Clin Endocrinol Metab.* 2004;89(10):5003-5012.

48. Follin C, Thilen U, Osterberg K, Bjork J, Erfurth EM. Cardiovascular risk, cardiac function, physical activity, and quality of life with and without long-term growth hormone therapy in adult survivors of childhood acute lymphoblastic leukemia. *J Clin Endocrinol Metab.* 2010;95(8):3726-3735.

49. Gleeson HK, Stoeter R, Ogilvy-Stuart AL, Gattamaneni HR, Brennan BM, Shalet SM. Improvements in final height over 25 years in growth hormone (GH)-deficient childhood survivors of brain tumors receiving GH replacement. *J Clin Endocrinol Metab.* 2003;88(8):3682-3689.

50. Murray RD, Darzy KH, Gleeson HK, Shalet SM. GH-deficient survivors of childhood cancer: GH replacement during adult life. *J Clin Endocrinol Metab.* 2002;87(1):129-135.

51. Cohen LE, Gordon JH, Popovsky EY, et al. Bone density in post-pubertal adolescent survivors of childhood brain tumors. *Pediatr Blood Cancer.* 2012;58(6):959-963.

52. Nyberg F, Hallberg M. Growth hormone and cognitive function. *Nat Rev Endocrinol.* 2013;9(6):357-365.

53. Krull KR, Li C, Phillips NS, et al. Growth hormone deficiency and neurocognitive function in adult survivors of childhood acute lymphoblastic leukemia. *Cancer.* 2019.

54. Tamhane S, Sfeir JG, Kittah NEN, et al. GH Therapy in Childhood Cancer Survivors: A Systematic Review and Meta-Analysis. *J Clin Endocrinol Metab.* 2018;103(8):2794-2801.

55. Taylor PN, Razvi S, Pearce SH, Dayan CM. Clinical review: A review of the clinical consequences of variation in thyroid function within the reference range. *J Clin Endocrinol Metab.* 2013;98(9):3562-3571.

56. Carter J, Lacchetti C, Andersen BL, et al. Interventions to Address Sexual Problems in People With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Adaptation of Cancer Care Ontario Guideline. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2017:Jco2017758995.

57. World Health Organisation. Sexual health - a new focus for WHO: progress in reproductive health research. http://www.who.int/hrp/publications/progress67.pdf. (accessed november 14, 2017).

58. Bober SL, Zhou ES, Chen B, Manley PE, Kenney LB, Recklitis CJ. Sexual function in childhood cancer survivors: a report from Project REACH. *The journal of sexual medicine.* 2013;10(8):2084-2093.

59. Zebrack BJ, Foley S, Wittmann D, Leonard M. Sexual functioning in young adult survivors of childhood cancer. *Psycho-oncology.* 2010;19(8):814-822.

60. Kubin M, Wagner G, Fugl-Meyer AR. Epidemiology of erectile dysfunction. *Int J Impot Res.* 2003;15(1):63-71.

61. Ritenour CW, Seidel KD, Leisenring W, et al. Erectile Dysfunction in Male Survivors of Childhood Cancer-A Report From the Childhood Cancer Survivor Study. *J Sex Med.* 2016;13(6):945-954.

62. Shamloul R, Ghanem H. Erectile dysfunction. *Lancet (London, England).* 2013;381(9861):153-165.

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De overlevingskans van kinderen met kanker is de laatste decennia toegenomen tot boven de 80%. Hierdoor ontstaat een groeiend cohort kinderen die kanker heeft overleefd. Deze kinderen hebben gedurende hun leven een groot risico op het ontwikkelen van gezondheidsproblemen door de tumor zelf of de tumorbehandeling. Dit proefschrift richt zich met name op gezondheidsproblemen als gevolg van schade aan de geslachtsorganen, hypothalamus en/of hypofyse; een klein gebied middenin de hersenen verantwoordelijk voor homeostase en de hormoonhuishouding. Disfunctioneren van de geslachtsorganen, hypothalamus en/of hypofyse kan gevolgen hebben voor lichaamsgroei, puberteitsontwikkeling en mentale en fysieke gezondheid. Omdat hormonale disfunctie vaak goed behandelbaar is en daarmee de consequenties mogelijk voorkomen kunnen worden, is vroegtijdige opsporing erg belangrijk. Dit proefschrift beschrijft de prevalentie, risicofactoren en klinische gevolgen van hypothalame-hypofyse disfunctie en gonadale disfunctie bij mannen na behandeling voor kinderkanker en tumoren in het centrale zenuwstelsel.

Deel I Hypothalame obesitas na behandeling voor een craniopharyngeoom of andere suprasellaire tumoren

Honger- en verzadigingsgevoel worden gereguleerd door een klein gebied in de hersenen: de hypothalamus. De hypothalamus ontvangt signalen van het lichaam over de voedingsstatus. Schade aan de hypothalamus door een hersentumor in dat gebied, een craniopharyngeoom of andere tumor, zorgt ervoor dat deze signalen niet meer goed aankomen. Daardoor denkt het brein dat je honger hebt en zendt het constant signalen uit die het hongergevoel stimuleren, ook al heb je net gegeten. Dit leidt tot een onverzadigbare eetlust en 'hypothalame obesitas'; een vorm van extreem overgewicht die moeilijk te behandelen is. In *hoofdstuk 2* zagen we dat hypothalame obesitas vaak voorkwam (54.3%) bij patiënten met een craniopharyngeoom, een goedaardige tumor in de hypofyse. Patiënten bij wie de tumor volledig was weggehaald, hadden een grotere kans op het ontwikkelen van hypothalame obesitas, vergeleken met een tumor die gedeeltelijk was weggehaald. Echter, overgewicht bij diagnose bleek de belangrijkste voorspeller voor de ontwikkeling van *morbide* obesitas, onafhankelijk van de grootte van de neurochirurgische ingreep. Daarnaast bleek het craniopharyngeoom vaker terug te keren bij patiënten met een gedeeltelijke tumorresectie, terwijl patiënten met een volledige tumorresectie meer hormonale stoornissen ontwikkelden. Voor iedere patiënt zal behandeling en nazorg dus geïndividualiseerd moeten worden om zowel terugkeer van de tumor, als hormonale stoornissen en obesitas te voorkomen.

Hypothalame obesitas als gevolg van een craniopharyngeoom of een andere tumor in het hypothalame/hypofyse gebied is erg lastig te behandelen; patiënten hebben naast een onverzadigbare eetlust, ook een verlaagd energiemetabolisme. In *hoofdstuk 3* beschrijven we

mechanismen die bijdragen aan hypothalame obesitas en daarnaast ook alle psychosociale, dieet, medicamenteuze en chirurgische interventies die ooit zijn uitgevoerd bij patiënten met verworven hypothalame obesitas. Alhoewel in het algemeen de interventies niet effectief waren om hypothalame obesitas te behandelen, bleken sommige interventies toch te werken bij individuele patiënten. Met die gedachte hebben we op basis van de pathofysiologische mechanismen en zes klinische domeinen (*i.e.*, psychosociale stoornissen, excessieve eetdrang, slaapstoornissen, verlaagd energieverbruik, hyperinsulinemie en hypofyse uitval) een gepersonaliseerd behandelplan gemaakt voor hypothalame obesitas.

De behandeling van obesitas, ook in de algemene bevolking, start vaak met het veranderen van het voedingspatroon om daarmee de totale calorie inname te verminderen. In *hoofdstuk 3* bleek dat slechts één studie de effectiviteit van een dieetinterventie voor hypothalame obesitas had onderzocht. Omdat het aanpassen van het voedingspatroon een mogelijke behandelmogelijkheid is, beschrijven we in *hoofdstuk 4* de resultaten van een pilotstudie bij zes kinderen met hypothalame obesitas. Gedurende een jaar volgden deze kinderen een individueel eetplan (het Stippenplan), gecombineerd met een intensief coachingstraject. Alhoewel de body mass index (BMI) van de kinderen in het begin van de interventie daalde, was er na 1 jaar follow-up geen verschil meer in BMI. Echter, twee kinderen was het wel gelukt om na 1 jaar blijvend af te vallen. Hoewel de interventie over het algemeen niet effectief leek op het gebied van BMI reductie, werd het coachingstraject door de kinderen en ouders als positief ervaren. Daarnaast ervaarden zij ook meer inzicht en toename van kennis op het gebied van voeding, wat zij gedurende hun leven als jongvolwassene en volwassene kunnen gebruiken.

Deel II Hypothalame-hypofyse disfunctie na behandeling van kinderkanker

Het gebied waarin de hypothalamus en hypofyse zich bevinden, ook wel het suprasellaire gebied genoemd, kan beschadigd raken waardoor hypothalame-hypofyse disfunctie ontstaat. Hierdoor kan een tekort aan groeihormoon, schildklierhormoon, stresshormoon of puberteitshormoon of een te vroege puberteitsontwikkeling (*i.e.,* pubertas praecox) ontstaan. In het tweede deel van deze thesis focussen we ons op de prevalentie, risicofactoren en klinische gevolgen van hormonale disfunctie.

In twee verschillende cohorten hebben we dit onderzocht: een cohort bestaande uit 355 kinderen behandeld met bestraling tussen 1996-2016, met een huidige leeftijd van ~18 jaar (*hoofdstuk 5*), en een ouder cohort bestaande uit 3141 overlevenden van kinderkanker die zijn behandeld vanaf de jaren ’60 met een huidige leeftijd van ~30 jaar (*hoofdstuk 6*). *Hoofdstuk 5* illustreert duidelijk dat een hoge dosis bestraling op het hoofd of een tumor in het suprasellaire gebied een hoog risico geeft op hormonale disfunctie. Door de systematische en frequente endocriene follow-up, werd duidelijk dat hormonale disfunctie vaak al in de eerste jaren na behandeling

voor kinderkanker ontstaat, maar ook nog steeds kan ontwikkelen na langere tijd. In *hoofdstuk 6* bevestigen we dat craniale bestraling een grote risicofactor is voor hormonale disfunctie, maar toonden we aan dat ook lagere doses bestraling en chemotherapie ook een risico kunnen geven op hormonale disfunctie. Daarnaast laten we zien dat bijkomende hersenschade veroorzaakt door epilepsie, hydrocephalus met shunt plaatsing of vasculaire schade ook geassocieerd zijn met hormonale disfunctie. In beide cohorten zagen we dat hormonale disfunctie negatieve effecten kan hebben op groei, botdichtheid, gewicht en kwaliteit van leven. Daarnaast zagen we ook associaties tussen hormonale disfunctie en verminderde neurocognitieve functies, bijvoorbeeld intelligentie, geheugen en aandacht. Het is onduidelijk of hormonale disfunctie echt de oorzaak is van verminderd neurocognitief functioneren, of dat er andere factoren meespelen zoals bestraling of hersenschade.

Een tekort aan schildklierhormoon door hypothalame en/of hypofyse disfunctie, ook wel centrale hypothyreoïdie genoemd, kan ontstaan na bestraling van een hersentumor. Deze diagnose wordt vaak gesteld op basis van een te laag schildklierhormoon, ook wel vrij thyroxine (free thyroxine, FT4) genoemd. De afkapwaarde van een te laag schildklierhormoon is vaak gebaseerd op waarden in een gezonde populatie, waarbij geen rekening wordt gehouden met het beloop van individuele FT4-waarden in de tijd. In *hoofdstuk 7* laten we zien dat kinderen die zijn gediagnosticeerd met centrale hypothyreoïdie na craniale bestraling, al een dalende trend van FT4-waarden hadden voor de diagnose werd gesteld. Daarnaast hadden sommige kinderen waarbij geen centrale hypothyreoïdie was vastgesteld, ook een dalende trend van FT4-waarden. In *hoofdstuk 8* bevestigen we dat FT4-waarden dalen na craniale bestraling, in een cohort kinderen waarbij systematisch en frequent FT4-waarden werden gemeten. In dit cohort konden we bovendien aantonen dat lagere of dalende FT4-waarden geassocieerd waren met negatieve effecten op groei, gewicht en metabole gezondheid. De volgende stap is om te kijken of we met variaties en trends van FT4-waarden de diagnose centrale hypothyreoïdie ook kunnen vaststellen, en of kinderen met dalende FT4-waarden na bestraling al baat hebben bij behandeling met schildklierhormoon (levothyroxine).

In *hoofdstuk 9* presenteren we aanbevelingen voor screening op hypothalame-hypofyse disfunctie in overlevenden van kinderkanker. Deze aanbevelingen zijn gebaseerd op resultaten van gepubliceerde studies en klinische expertise van een internationaal panel, bestaande uit 42 experts. Met internationale richtlijnen kunnen we de screening op hypothalame-hypofyse disfunctie in overlevenden van kinderkanker uniformeren, om zo gezondheidsproblemen in deze groep te voorkomen of verminderen.

Deel III Hypogonadisme bij mannen na behandeling van kinderkanker

De testes hebben, naast het produceren van zaadcellen, als andere belangrijke functie het maken van testosteron door de Leydig cellen. De invloed van chemotherapie en bestraling op de functionaliteit van deze Leydig cellen en de fysieke, psychosociale en seksuele gevolgen van een tekort aan geslachtshormonen door Leydig cel disfunctie, hebben wij onderzocht in *hoofdstuk 10.* In een cohort van 1534 mannen (gemiddeld 22 jaar na hun behandeling) waren bestraling op de testes en chemotherapie geassocieerd met Leydig cel disfunctie. De mannen die leden aan Leydig cel disfunctie, hadden ook vaker fysieke, psychosociale en seksuele klachten, zoals obesitas, depressie en erectiele disfunctie. Bovendien bleek van de geïncludeerde 1021 mannen die kinderkanker hadden overleefd, 29% erectiele disfunctie te hebben (*hoofdstuk 11*). Erectiele disfunctie bij deze mannen was sterk geassocieerd met lage testosteron waarden, mogelijk door directe schade aan de testes (*i.e.,* Leydig cel disfunctie) of schade aan de hypothalamus en/of hypofyse (*i.e.,* hypogonadotroop hypogonadisme). Of tijdige behandeling met testosteron deze fysieke, psychosociale en seksuele klachten kan verbeteren, zal in nieuwe studies moeten worden onderzocht.

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In this thesis

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van Iersel L., Brokke K.E., Adan R.A.H., Bulthuis L.C.M., van den Akker E.L.T., van Santen, H.M. Pathophysiology and Individualized Treatment of Hypothalamic Obesity Following Craniopharyngioma and Other Suprasellar Tumors: A Systematic Review. *Endocrine Reviews*. 2018;4(1):193-235

van Iersel L., Veen-Roelofs J., Heeren J., Takken T., Grootenhuis M.A., van der Torre P., van Santen H.M. Feasibility and Effectiveness of an Individualized Dietary Intervention for Children with Acquired Hypothalamic Obesity: A Pilot Study. *Submitted*

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van Iersel L., Xu J., Potter B., Conklin H.M., Zhang H., Chemaitilly W., van Santen H.M., Merchant T.E. Clinical Significance of Variation in Free Thyroxine Concentrations after Radiation Therapy for Pediatric Brain Tumors: A Longitudinal Study. *Submitted*

van Iersel L., Mulder R.L., Wallace W.H., Constine L.S., Skinner R., Hudson M.M., Kremer L.C.M., Chemaitilly W., van Santen H.M. Recommendations for Surveillance of Hypothalamic-Pituitary Dysfunction for Childhood, Adolescent and Young Adult Cancer Survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Manuscript in progress*

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van Iersel L., Li Z., Chemaitilly W., Schover L.R., Ness K.K., Hudson M.M., Klosky J.L. Erectile Dysfunction in Male Survivors of Childhood Cancer. *JAMA Oncology*. 2018;4(11):1613–1616

Other publications

van Iersel L, van Someren F., Teuwen G.J., de Bruin T., van Meersbergen D. BIG-herregistratie van arts-onderzoekers verzekerd. *Nederlands Tijdschrift voor Geneeskunde*. 2016;160:B1257

van Iersel L., van Santen H.M., Zandwijken G.R.J., Zwaveling-Soonawala N., Hokken-Koelega A.C.S., van Trotsenburg A.S.P. Low FT4 concentrations around the start of rhGH treatment: predictor of congenital structural HP abnormalities? *Hormone Research Paediatrics*. 2018;89:98–107

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Curriculum vitae

Laura van Iersel was born on May 29th, 1989 in Boxtel, the Netherlands. She graduated from secondary school in 2007 at the Jacob-Roelandslyceum in Boxtel. In that year, she started her study Medicine at the Academic Medical Center (AMC), University of Amsterdam. She interrupted this study in 2008-2009 for a first-year Biology at the University of Groningen which she completed cum laude. During her medical studies, she developed an interest in pediatric endocrinology and therefore started a research project at the Pediatric Endocrinology department, supervised by Prof. dr. A.S. Paul van Trotsenburg and dr. H.M. van Santen. In addition, she completed an international rotation pediatric palliative care in Queen Elizabeth Central Hospital in Blantyre (Malawi) and volunteered in Kumasi (Ghana) and Masaka (Uganda).

After graduating from medical school in 2015, Laura started her PhD trajectory, resulting in this thesis, at the department of Pediatric Endocrinology at the Wilhelmina Children's Hospital (WKZ), supervised by Prof. dr. E.E.S. Nieuwenhuis and dr. H.M. van Santen. For her work on the longitudinal follow-up of hypothalamic-pituitary-thyroid function in childhood brain tumor survivors, Laura received the price for best abstract at the International Pituitary Congress in 2017. With financial support of the Ter Meulen grant of the The Royal Netherlands Academy of Arts and Sciences and Stichting Kinderen Kankervrij, Laura performed a research rotation at St. Jude Children's Research Hospital, Memphis, Tennessee, USA between November 2017 and October 2018, supervised by dr. W. Chemaitilly. During her PhD trajectory, Laura was a board member of the PhD candidates Network of the Netherlands and Young Dutch Society for Endocrinology. In 2016 she co-founded the WKZ research committee to enhance collaboration between clinicians and researchers in Pediatrics.

In March 2019, Laura started working as a resident pediatrics (not in training) at the WKZ. Laura lives together with Laurens Sand in Utrecht, the Netherlands.